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(71) Applicants (for all designated States except US):
DANA-FARBER CANCER INSTITUTE, INC.
[US/US]; 44 Binney Street, Boston, MA 02115 (US).
TRUSTEES OF BOSTON UNIVERSITY [US/US]; 147
Bay State Road, Boston, MA 02215 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SCHULTZE,**

Joachim, L. [DE/US]; 37 Auburn Street, Brookline, MA 02146 (US). **VONDERHEIDE, Robert, H.** [DE/US]; Apartment 801, 1284 Beacon Street, Brookline, MA 02115 (US). **SHERR, David** [US/US]; 39 Hastings Street, West Roxbury, MA 02132 (US). **NADLER, Lee, M.** [US/US]; 36 Cross Hill Road, Newton, MA 02159 (US). **MAECKER, Britta** [DE/US]; 368 Longwood Avenue, #21, Boston, MA 02215 (US). **VON BERGWELT-BAILDON, Michael** [DE/US]; 24 A Prentiss Street, Cambridge, MA 02140 (US).

(74) Agent: **CLARK, Paul, T.**; Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110-2214 (US).

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(54) Title: CANCER IMMUNOTHERAPY AND DIAGNOSIS USING CYTOCHROME P450 1B1

(57) Abstract: The invention provides methods for conducting cancer immunotherapy and diagnosis using cytochrome P450 1B1 and peptide fragments thereof.

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CANCER IMMUNOTHERAPY AND DIAGNOSIS USING
CYTOCHROME P450 1B1

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Background of the Invention

This invention relates to the prevention, treatment, and diagnosis of cancer.

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The paucity of clinically significant anti-tumor immune responses in cancer patients has long suggested that antigen-specific immunotherapy would not play a significant role in cancer treatment. However, pioneering studies in the early 1990s, using tumor-specific cytotoxic T lymphocytes (CTLs) from cancer patients, showed the existence of human tumor associated antigens (TAAs). This led to the suggestion that such antigens could be used to stimulate therapeutic anti-tumor immune responses in patients. Although these studies focused primarily on melanoma, TAAs have also been characterized in several other malignancies (Van Pel *et al.*, Immunological Reviews 145:229-250, 1995; Rosenberg, Immunol. Today 18:175-182, 1997; Van den Eynde *et al.*, Curr. Opin. Immunol. 9:684-693, 1997), raising the hypothesis that most, if not all, tumors express antigens that can be used to induce CTL-mediated tumor destruction. Consequently, clinical efforts are now underway to target TAAs in strategies, such as vaccination and adoptive T cell therapy, to generate effective anti-tumor CTL responses in patients.

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The demonstration that TAA-specific immune responses can lead to tumor regression has been borne out extensively in animal models (Rosenberg, Immunity 10:281-287, 1999). Although the identification of TAAs using patients' CTLs has revitalized the field of T cell immunotherapy, these methods are slow, very expensive, and labor-intensive. Moreover, the strategy relies on the generation of tumor-specific T cell clones *in vitro*, suggesting that only a restricted set of TAAs will be identified by this method. With these limitations in mind, Pfreundschuh and colleagues developed an alternative approach, SEREX

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(serological identification of antigens by recombinant expression cloning), to identify TAAs (Sahin *et al.*, Curr. Opin. Immunol. 9:709-716, 1997). SEREX makes use of patients' antibody responses to tumor-derived genes and this strategy has accelerated the identification of TAAs significantly. Although
5 several T cell-defined TAAs, such as the MAGE genes, have also been identified by SEREX, there is no information available about CTL epitopes for the vast majority of genes in the SEREX database, and, of course, such epitopes are required to activate a CTL response.

Although there is no doubt that the identification of numerous TAAs by
10 CTL-based approaches or SEREX reflects the existence of an anti-tumor immune response, it remains to be determined if these antigens play a role as tumor regression antigens (Sarma *et al.*, J. Exp. Med. 189:811-820, 1999). Indeed, most T cell epitopes in TAAs identified by patient CTLs have been demonstrated to be of low MHC binding affinity and/or low MHC/peptide complex stability. This
15 quality distinguishes TAA-derived peptides from viral peptides that are almost exclusively of high binding affinity and high MHC/peptide complex stability (Feltkamp *et al.*, Mol. Immunol. 31:1391-1401, 1994; Sette *et al.*, J. Immunol. 153:5586-5592, 1994). Clinical vaccination trials have circumvented this obstacle by utilizing altered peptides with higher MHC binding affinity and
20 higher MHC/peptide complex stability (Rosenberg *et al.*, Nat. Med. 4:321-327, 1998). The low binding affinity of TAA-derived peptides is likely to be one of the reasons why natural CTL responses against such peptides are not successful for tumor eradication. This is in agreement with the finding that large numbers of TAA-specific CTLs co-exist with metastatic tumors in melanoma patients
25 (Romero *et al.*, J. Exp. Med. 188:1641-1650, 1998). A recent study has even demonstrated that despite expansion, such CTLs were hyporesponsive, showing reduced cytotoxic and cytokine responses (Lee *et al.*, Nat. Med. 5:677-685, 1999).

In addition, most TAAs described thus far are expressed in only one or a few tumor types, and not all patients with a given tumor type express the
30 associated TAA. As a result, progress in the field of cancer immunotherapy has been relatively slow, because it has not been possible to develop widely useful

TAA-specific immunotherapeutic strategies. Not only has it been necessary to tailor such therapies to individual types of malignancies, in some cases (such as the immunoglobulin idiotypic antigen in B cell malignancies), it has been necessary to tailor these therapies to individual patients.

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Summary of the Invention

The invention provides a method of treating a patient that has or is at risk of having a cell that expresses cytochrome P450 1B1 (CYP1B1). This method involves administering to the patient a cytotoxic T lymphocyte (CTL)(autologous or allogeneic) that leads to death of (from here on said as kill) the cell in a CYP1B1-specific, major histocompatibility complex-restricted fashion. The CTL can be generated, for example, by activation with an antigen presenting cell that has been pulsed with CYP1B1, or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule.

15 The invention also includes a second method of treating a patient that has or is at risk of having a cell that expresses CYP1B1. This method involves administering to the patient an antigen presenting cell (APC) that activates in the patient a cytotoxic T lymphocyte that kills the cell in a CYP1B1-specific, major histocompatibility complex-restricted fashion. The APC can be pulsed with CYP1B1 or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule.

20 Another method included in the invention is a third method of treating a patient that has or is at risk of having a cell that expresses CYP1B1. This method involves administering to the patient CYP1B1 or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule, which is processed by an antigen presenting cell in the patient, which, in turn, activates a cytotoxic T lymphocyte in the patient to induce cell death of the cell that expresses CYP1B1 in a CYP1B1-specific, major histocompatibility complex-restricted fashion. The CYP1B1 polypeptide or peptide of CYP1B1 used in this method can be administered to the patient in association with an adjuvant.

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The invention also includes a fourth method of treating a patient that has or is at risk of having a cell that expresses CYP1B1. This method involves administering to the patient a nucleic acid molecule encoding CYP1B1 or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule.

5 The nucleic acid molecule is expressed in the patient so that it can be processed by an antigen presenting cell in the patient, which activates a cytotoxic T lymphocyte in the patient to induce cell death of the cell that expresses CYP1B1, in a CYP1B1-specific, major histocompatibility complex-restricted fashion. The nucleic acid molecule encoding CYP1B1 or a peptide of CYP1B1 can be present
10 in an expression vector.

Each of the methods described above can also include treatment based around a second (or more) tumor associated antigen, *e.g.*, telomerase (hTERT, PCT/US99/25438), or a peptide thereof that binds to MHC (*e.g.*, the I540 peptide).

15 In any of the methods described above, the patient can have a tumor containing cells that express CYP1B1. APCs used in these methods can be, for example, a dendritic cell or a CD40-activated B cell. The peptide of CYP1B1 in these methods can bind to a class I or a class II major histocompatibility complex (MHC) molecule. In the case of a class I MHC molecule, the molecule can be,
20 for example, an HLA-A2 molecule, and the peptide of CYP1B1 can include the amino acid sequence of CYP239 (SEQ ID NO:1; SLVDVMPWL), CYP246 (SEQ ID NO:2; WLQYFPNPI), CYP190 (SEQ ID NO:3; FLDPRPLTV), or CYP528 (SEQ ID NO:4; LLDSAVQNL). Examples of other CYP1B1 sequences that can be used in these methods are set forth in the Sequence Appendix and in Tables 3-
25 10.

The invention also includes a method of assessing the level of immunity of a patient to CYP1B1 or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule. In this method, the level of cytotoxic T lymphocytes specific for CYP1B1 or a peptide of CYP1B1 is measured in a
30 sample from a patient. The sample can be obtained from the patient before,

during, or after a cancer treatment is administered to the patient. A sample can also be obtained, for example, before and after treatment.

The invention also includes CYP1B1 peptides that bind to major histocompatibility complex molecules, for example, a peptide that consists essentially of the amino acid sequence set forth in SEQ ID NO:1 (CYP239), SEQ
5 ID NO:2 (CYP246), SEQ ID NO:3 (CYP190), or SEQ ID NO:4 (CYP528).

Also included in the invention is an *ex vivo* generated cytotoxic T lymphocyte that specifically kills a cell expressing CYP1B1 in a specific, major histocompatibility complex-restricted fashion, and an *ex vivo* generated antigen
10 presenting cell (*e.g.*, a dendritic cell or a CD40-activated B cell) that presents a peptide of CYP1B1 in the context of a major histocompatibility complex molecule.

As is understood in the art, a "polypeptide" is a chain of amino acids linked to one another by peptide bonds. A "protein" can be made up of one or
15 more polypeptides, while a "peptide" is generally understood to be (or include) a fragment of a polypeptide, and to consist of a chain of peptide bond-linked amino acids that is shorter in length than a full length polypeptide from which it may be derived.

A "tumor associated antigen," such as CYP1B1, is an immunogenic
20 molecule, such as a protein, that is, generally, expressed at a higher level in tumor cells than in non-tumor cells, in which, preferably, it may not be expressed at all, or only at low levels. A tumor associated antigen, or TAA, is said to be "universal" if it is expressed in tumors of different origins.

A "cytochrome P450 1B1 polypeptide," or a "CYP1B1 polypeptide" is
25 a full length, non-fragmented polypeptide of CYP1B1, while a "cytochrome P450 1B1 peptide," or a "CYP1B1 peptide," is (or includes) a fragment of such a CYP1B1 polypeptide. CYP1B1 peptides can be of any length, up to just under the full length of a CYP1B1 polypeptide. However, preferably, for use in the invention, CYP1B1 peptides are of a relatively short length, such as, for example,
30 eight, nine, ten, eleven, or twelve amino acids. Also, a CYP1B1 peptide may include sequences that are not present in a corresponding CYP1B1 polypeptide,

provided that the CYP1B1 peptide also includes a stretch of at least, for example, eight, nine, ten, eleven, or twelve consecutive amino acids that have a sequence that is identical to a sequence of eight, nine, ten, eleven, or twelve consecutive amino acids in a CYP1B1 polypeptide.

5 Peptides including amino acid substitutions can also be considered as CYP1B1 peptides. For example, a CYP1B1 peptide can include a region of at least nine amino acids, of which any six or more are identical to the amino acids within a nine amino acid stretch in CYP1B1. Preferably, at least seven, more preferably, at least eight, and, most preferably, all nine of the amino acids in a
10 CYP1B1 peptide nine amino acid region are identical to a nine amino acid region in the CYP1B1.

A CYP1B1 polypeptide corresponding to CYP1B1 includes 533 amino acids that are substantially identical (see below) to the amino acid sequence of CYP1B1 (Sutter *et al.*, J. Biol. Chem. 269:13092-13099, 1994; Tang *et al.*, J.
15 Biol. Chem. 271:28324-28330, 1996; Genbank Accession No. U56438), or such a polypeptide can include the amino acid sequence of CYP1B1, as well as additional sequences.

As is discussed further below, it is preferable that CYP1B1 polypeptides of the invention include regions that bind to major histocompatibility
20 complex (MHC) antigens. Preferred examples of CYP1B1 peptides that are included in the invention are CYP239 (SEQ ID NO:1), CYP246 (SEQ ID NO:2), CYP190 (SEQ ID NO:3), and CYP528 (SEQ ID NO:4). Additional CYP1B1 peptides are listed in the Sequence Appendix, as well in Tables 3-10, and still more CYP1B1 peptides can be identified using methods described below (also see
25 PCT/US99/25438).

A CYP1B1 peptide or polypeptide can be fused to amino acid sequences that do not naturally occur in CYP1B1. Moreover, a CYP1B1 peptide or polypeptide can be attached to the surface of a cell or to a molecule or a macromolecule (*e.g.*, a histocompatibility antigen), or a CYP1B1 peptide or
30 polypeptide can be conjugated to immunogens or adjuvants that are known to those of skill in this art, for example, keyhole limpet hemocyanin (KLH), for the

purpose of eliciting a CYP1B1-specific immune response. As is noted above, preferred examples of CYP1B1 peptides are CYP239 (SEQ ID NO:1), CYP246 (SEQ ID NO:2), CYP190 (SEQ ID NO:3), and CYP528 (SEQ ID NO:4).

By "CYP1B1 nucleic acid molecule" is meant a DNA or RNA (*e.g.*, mRNA) molecule that encodes a CYP1B1 polypeptide or CYP1B1 peptide, as are defined above.

By "CYP1B1-expressing tumor cell" is meant a tumor cell that expresses CYP1B1. A CYP1B1-expressing tumor cell can express a level of CYP1B1 that is equal to, or, preferably, greater than the level of CYP1B1 expressed by the normal cell type from which the CYP1B1-expressing tumor cell has originated, or other non-tumor cells. Preferably, the tumor cell expresses at least 10% more CYP1B1, more preferably, at least 25% more, still more preferably at least 50% more, and most preferably at least 150% more CYP1B1 than the normal cell type from which the CYP1B1-expressing tumor cell has originated, or another non-tumor cell. CYP1B1 expression levels in a CYP1B1-expressing tumor cell can be increased by, for example, increased transcription of the CYP1B1 gene, increased CYP1B1 mRNA stability or translation, increased CYP1B1 polypeptide stability, or increased CYP1B1 enzymatic activity. Increasing such CYP1B1 expression levels may be useful in the invention to increase the likelihood that a tumor cell will be recognized as a target of the immunotherapeutic methods described herein (see below).

By "histocompatibility antigen" is meant a molecule, such as a major histocompatibility complex (MHC) class I, MHC class II, or minor histocompatibility antigen, that mediates interactions of cells of the immune system with each other and with other cell types. Examples of histocompatibility antigens include MHC class I antigens, such as HLA-A (*e.g.*, A1, A2, A3, A11, A24, A31, A33, and A38), HLA-B, and HLA-C, MHC class II antigens, such as HLA-DR, HLA-DQ, HLA-DX, HLA-DO, HLA-DZ, and HLA-DP, and minor histocompatibility antigens, such as HA-1.

By “generating CTLs” is meant an *in vivo*, *in vitro*, or *ex vivo* process by which CTLs (*e.g.*, CYP1B1-specific CTLs) are activated (*e.g.*, stimulated to grow and divide) and/or selected.

A peptide of CYP1B1 is said to “specifically bind” to an MHC antigen if the peptide adheres to a histocompatibility antigen under physiological conditions. For example, such binding can be similar to that of a peptide antigen that is naturally processed and presented in the context of MHC in an antigen presenting cell.

A cytotoxic T lymphocyte (CTL) or antibody is said to “specifically recognize” a CYP1B1 polypeptide or a CYP1B1 peptide if it binds to the polypeptide or peptide, but does not substantially bind to other, unrelated polypeptides or peptides.

A CTL is said to “specifically kill” a cell if it specifically recognizes and lyses a cell that expresses an antigen (*e.g.*, CYP1B1) to which it has been activated, but does not substantially recognize or lyse cells not expressing the antigen. In the case of CYP1B1, such a CTL is designated as a “CYP1B1-specific CTL” herein.

By “CYP1B1-specific antibody” is meant an antibody that can specifically recognize and bind to a CYP1B1 peptide or polypeptide, and that does not substantially recognize and bind to other, unrelated molecules.

A CYP1B1 polypeptide is “presented” if a peptide of CYP1B1 is displayed on the extracellular surface of a cell (*e.g.*, an antigen presenting cell), such that it can result in the *in vivo*, *ex vivo*, or *in vitro* generation of CYP1B1-specific CTLs or the lysis of a tumor cell by a CYP1B1-specific CTL. Preferably, the displayed CYP1B1 peptide is bound to a histocompatibility antigen.

By “physiological conditions” is meant the *in vivo* environment in which CYP1B1-specific CTLs are generated (activated and/or selected) and perform their biological functions (*e.g.*, recognition of a CYP1B1 peptide and MHC-restricted lysis of CYP1B1-expressing tumor cells), or an *in vitro* or *ex vivo* environment that allows CYP1B1-specific CTLs to be generated and to perform their biological functions.

By "CYP1B1 vaccination" is meant administration of an immunogenic preparation including one or more CYP1B1 peptides, CYP1B1 polypeptides, CYP1B1 nucleic acid molecules, fragments of any of these molecules, CYP1B1-presenting cells (*e.g.*, dendritic cells or CD40-activated B cells), or mixtures thereof. Vaccination is performed on a subject who has a tumor, has a history of having a tumor or tumors, is likely to develop a tumor, or any healthy individual to prevent tumors, or on a subject in which CYP1B1-specific immune cells (such as CTLs) are to be generated for transfer into a patient. Such vaccination stimulates a CYP1B1-specific immune response within the subject. In subjects having tumors, the vaccination can result in partial or complete inhibition of tumor growth, or partial or complete tumor regression, provided that the patient's tumor expresses CYP1B1. In addition, vaccination can provide prophylaxis against the development of new CYP1B1-expressing tumors.

A "vaccine," as used herein, is an immunogenic composition that can be administered in the vaccination method described above. Thus, a vaccine includes, for example, one or more CYP1B1 peptides, CYP1B1 polypeptides, CYP1B1 nucleic acid molecules, fragments of any of these molecules, CYP1B1-presenting cells (*e.g.*, dendritic cells or CD40-activated B cells), or mixtures thereof. Optionally, a vaccine composition can also include an adjuvant, which is a molecule that stimulates an immune response to a co-administered vaccine antigen. Examples of adjuvants that can be used in the invention are provided below. A vaccine composition can also include other tumor associated antigens (*e.g.*, hTERT) or peptides thereof (PCT/US99/25438).

By "immune cell" is meant any cell that plays a role in cell-mediated or humoral immunity, including CTLs and antigen-presenting cells, *e.g.*, B cells, T helper cells, and dendritic cells.

By "sample" is meant a tumor or tissue biopsy, a lymph node biopsy, bone marrow, cells, blood, serum, urine, stool, sputum, saliva, or other specimen obtained from a patient. A sample can be analyzed to determine the level of CYP1B1-specific CTLs, the level of CYP1B1-specific antibodies, or the level of any other immune response indicator (*e.g.*, a cytokine) in the patient from whom

it was taken by methods that are known in the art. For example, ELISA can be used to measure levels of CYP1B1-specific antibodies, and ELISPOT can be used to measure cytokine levels. Also, Cr⁵¹ release (T cell cytotoxicity) assays and assays that test the binding of CTLs to tetrameric CYP1B1 peptide/MHC complexes, as described herein, can be used to measure levels of CYP1B1-specific CTLs.

By "reference sample" is meant a sample in which the level of CYP1B1-specific CTLs or the level of CYP1B1-specific antibodies have been measured, and to which the level of CYP1B1-specific CTLs or the level of CYP1B1-specific antibodies in a test subject's sample are compared. Reference levels can be higher, lower, or the same as patient sample levels. Comparison of a test sample to a reference sample provides an assessment of the CYP1B1-specific immune response in the test subject. In addition, comparison of a patient's sample levels to reference sample levels can allow a diagnosis of cancer and/or a prognosis of a cancer in a patient having a tumor that includes CYP1B1-expressing cells.

By "cancer treatment" is meant any therapy (*e.g.*, chemotherapy, radiation therapy, administration of a tumor associated antigen (*e.g.*, CYP1B1)-specific CTLs, administration of an APC presenting a peptide of a TAA (*e.g.*, CYP1B1), or vaccination with a TAA (*e.g.*, CYP1B1), a nucleic acid molecule encoding a TAA (*e.g.*, CYP1B1), or a fragment thereof, to enhance an anti-tumor immune response) administered either alone or in combination with other therapies, that alleviates disease in at least some patients to which the treatment is administered. For example, a cancer treatment can reduce or inhibit tumor growth, or can induce partial or complete tumor regression. Furthermore, a cancer treatment can be prophylactic, in that it inhibits or prevents the development of new tumors in healthy individuals, in patients that are in remission from cancer, have metastatic cancer, or have a high risk of developing cancer.

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By “inhibiting the development of a tumor” is meant administering a protective therapy (such as CYP1B1-specific CTLs, CYP1B1 peptide presenting APCs, or a vaccine including, for example, one or more CYP1B1 peptides, CYP1B1 polypeptides, or CYP1B1 nucleic acid molecules, or a combination thereof) to a subject adjudged to have a higher than average risk of developing a tumor. Subjects with a relatively high risk of developing a tumor include those having a family history of cancer, those having one or more genetic mutations that are associated with a high risk for cancer (e.g., a mutation that inactivates a tumor suppressor gene), those having relatively high levels of CYP1B1-specific CTLs or CYP1B1-specific antibodies, those who have cancer or are in remission from cancer, and those who have been exposed to agents known or suspected to cause cancer.

By “pharmaceutically acceptable carrier” is meant a carrier that is physiologically acceptable to a treated patient, while retaining the therapeutic properties of the compound with which it is administered. One exemplary pharmaceutically acceptable carrier is physiological saline. Other physiologically acceptable carriers and their formulations are known to those skilled in the art, and are described, for example, in *Remington's Pharmaceutical Sciences* (18th edition), ed. A. Gennaro, 1990, Mack Publishing Company, Easton, PA.

The term “substantially identical” is used herein to describe a polypeptide or nucleic acid molecule exhibiting at least 50%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% identity to a reference amino acid or nucleic acid sequence. For polypeptides, the length of comparison sequences is at least 8 amino acids, preferably at least 16 amino acids, more preferably at least 25 amino acids, and most preferably 35 amino acids. For nucleic acid molecules, the length of comparison sequences is at least 24 nucleotides, preferably at least 50 nucleotides, more preferably at least 75 nucleotides, and most preferably at least 110 nucleotides. Sequence identity is typically measured using sequence analysis software with the default parameters specified therein (e.g., Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710

University Avenue, Madison, WI 53705). The CYP1B1 polypeptides, peptides, and nucleic acid molecules of the invention can be identical or substantially identical to naturally occurring molecules, and thus may or may not include non-wild type sequences.

5 By "substantially pure peptide" or "substantially pure polypeptide" is meant a peptide, polypeptide, or a fragment thereof, which has been separated from the components that naturally accompany it. Typically, the peptide or polypeptide is substantially pure when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally
10 associated. Preferably, the peptide or polypeptide is a CYP1B1 peptide or polypeptide that is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, pure. A substantially pure CYP1B1 peptide or polypeptide can be obtained, for example, by extraction from a natural source (*e.g.*, a tumor cell), by expression of a recombinant nucleic acid molecule
15 encoding a CYP1B1 peptide or polypeptide, or by chemically synthesizing the peptide or polypeptide. Purity can be measured by any appropriate method, *e.g.*, by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

A protein is substantially free of naturally associated components when
20 it is separated from those contaminants that accompany it in its natural state. Thus, a protein that is chemically synthesized or produced in a cellular system different from the cell from which it naturally originates is substantially free from its naturally associated components. Accordingly, substantially pure peptides and polypeptides not only include those derived from eukaryotic organisms, but also
25 those synthesized in *E. coli* or other prokaryotes.

By "substantially pure DNA" or "isolated DNA" is meant DNA that is free of the genes that, in the naturally-occurring genome of the organism from which the DNA is derived, flank the gene. The term thus includes, for example, a recombinant DNA that is incorporated into a vector; an autonomously replicating
30 plasmid or virus; or the genomic DNA of a prokaryote or eukaryote; or DNA that exists as a separate molecule (*e.g.*, a cDNA, or a genomic or cDNA fragment

produced by PCR or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant DNA that is part of a hybrid gene encoding additional polypeptide sequence.

By “transformation,” “transfection,” or “transduction” is meant any method for introducing foreign molecules into a cell. Lipofection, DEAE-dextran-mediated transfection, microinjection, protoplast fusion, calcium phosphate precipitation, transduction (*e.g.*, bacteriophage, adenoviral retroviral, or other viral delivery), electroporation, and biolistic transformation are just a few of the methods known to those skilled in the art that can be used in the invention.

By “transformed cell,” “transfected cell,” or “transduced cell,” is meant a cell (or a descendent of a cell) into which a nucleic acid molecule (*e.g.*, a DNA or RNA molecule) encoding a polypeptide of the invention has been introduced by means of recombinant DNA techniques.

By “promoter” is meant a minimal sequence sufficient to direct transcription. Promoter elements that are sufficient to render promoter-dependent gene expression controllable for cell type-specific, tissue-specific, temporal-specific, or inducible by external signals or agents can also be used in the invention; such elements can be located in the 5' or 3' or intron sequence regions of the native gene.

By “operably linked” is meant that a gene and one or more regulatory sequences are connected in such a way as to permit gene expression when the appropriate molecules (*e.g.*, transcriptional activator proteins) are bound to the regulatory sequences.

By “expression vector” is meant a genetically engineered plasmid or virus, derived from, for example, a bacteriophage, adenovirus, retrovirus, poxvirus, herpesvirus, or artificial chromosome, that is used to transfer a peptide or polypeptide coding sequence (*e.g.*, a CYP1B1 peptide coding sequence), operably linked to a promoter, into a host cell, such that the encoded peptide or polypeptide is expressed within the host cell.

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Other features and advantages of the invention will be apparent from the drawings, following detailed description, and the claims.

Brief Description of the Drawings

- 5 Fig. 1 is a graph showing the level of peptide binding of MAGE-3, CYP239, and CYP246 to TAP-deficient T2 cells.
- Figs. 2A-2D are graphs showing that CTL derived from healthy donors recognize CYP239 and CYP246 peptides. (A) CTL raised against the CYP239 peptide specifically lyse CYP239 pulsed (■), but not unpulsed T2 cells (□), or T2 cells
- 10 pulsed with an irrelevant peptide (○; F271 from MAGE-3). (B) Similarly, CTL generated against the CYP246 peptide recognize only T2 cells pulsed with CYP246 (■), but not control T2 cells (□, unpulsed; ○, pulsed with F271). The diagrams display representative experiments for 11/13 healthy donors positive for CYP239-specific CTL induction and 4/10 healthy donors positive for CYP246-
- 15 specific CTL induction. (C) CYP239-specific CTL recognize autologous CD40-B cells pulsed with CYP239 peptide (◆), but not unpulsed autologous CD40-B (◇) or allogeneic HLA-A2 mismatched CD40-B unpulsed (○) or pulsed with CYP239 peptide (●). (D) Analogous results were obtained for CYP246-specific CTL using the same target cells unpulsed or pulsed with the CYP246 peptide.
- 20 Fig. 2E is a series of graphs showing a representative tetramer analysis of CYP239- and CYP246-specific CTL after 4 weeks in culture. The A2/TAX tetramer served as a negative control. Percent tetramer⁺ CD8⁺ T cells is shown. Positive tetramer staining correlated with specific cytotoxicity in ⁵¹Cr assays.
- Fig. 2F is a graph showing the cytotoxicity of expanded CYP239-specific
- 25 tetramer sorted CTL against T2 cells either unpulsed (□), pulsed with CYP239 (■) or RT-pol476 (○).
- Fig. 3 is a graph showing the level of specific lysis of CD40-activated B cells that were titrated with increasing concentrations of peptide before
- exposure to peptide-specific CTLs.

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Figs. 4A-4H are graphs showing that CYP239 and CYP246-specific CTL are cytotoxic for HLA-A2⁺ melanoma, multiple myeloma and ovarian carcinoma cell lines. Expression of CYP1B1 in all tumor cell lines was confirmed by Western blot analysis. HLA-A2⁺ cell lines are shown by solid symbols; HLA-A2⁻ cell lines by open symbols. Targets for CYP239-specific CTL (upper panel) and CYP246-specific CTL (lower panel) were (A, B) melanoma cell lines K029 (●) and SK-MEL-2 (○), (C, D) multiple myeloma cell lines U266 (●), IM-9 (◆) and HS-Sultan (◇), and (E, F) ovarian carcinoma cell lines 36M (■) and SK-OV-3 (□). Normal cells including the HLA-A2⁺ fibroblast cell line GM847 (Δ) and primary monocytes from 3 HLA-A2⁺ (○, ◇, ▽) and one HLA-A2⁻ healthy donors (□) were not lysed by either (G) CYP239-specific or (H) CYP246-specific CTL. Results of one representative experiment are shown. Similar results were obtained for each of 2 to 6 CTL tested per target.

Fig. 5 is a graph showing the specific lysis of tumor cells pulsed with CYP239 by CYP239-specific CTLs.

Figs. 6A-6C are graphs showing lysis of CYP1B1⁺ HLA-A2⁺ primary lymphoma and acute myeloid leukemia (AML). Two HLA-A2⁺ CYP1B1⁺ follicular lymphoma samples (■ and ●) from lymph node biopsies were lysed by (A) CYP239-specific and (B) CYP246-specific CTL, while no cytotoxicity occurred against an HLA-A2⁻ CYP1B1⁺ FL (□). Experiments were performed from two different normal donors with similar results. (C) CYP239-specific CTL lysed primary HLA-A2⁺ (◆), but not HLA-A2⁻ (◇) AML cells.

Figs. 7A and 7B are each a series of graphs showing the generation of CYP239- and CYP246-specific CTL from cancer patients. (A) CYP239-specific CTL from 4 patients (pt 1-4) and CYP246-specific CTL from pt 3 and pt 4 lysed T2 cells pulsed with the immunizing peptide (■), but not unpulsed T2 cells (□) or T2 cells pulsed with the irrelevant F271 peptide from MAGE-3 (○). (B) The same CYP239- or CYP246-specific CTL lysed the CYP1B1⁺ HLA-A2⁺ myeloma cell lines IM-9 (◆) and U266 (●) but not the CYP1B1⁻ HLA-A2⁻ line HS-Sultan (◇). In two cases, IM-9 cells were not lysed. All experiments shown here were performed twice with similar results.

Fig. 8 is a graph showing that the efficacy of a combination of CYP1B1 and hTERT-specific CTL in a chromium release assay. CYP239- and I540-specific CTL were used individually or in combination against a mixture of T2 cells pulsed with either CYP239 or I540 peptide. Target cells were mixed at a 1:1 ratio using a final number of 5000 cells/well. Numbers shown reflect the number of effector cells added to each well.

Fig. 9 is a graph showing the specific lysis of target cells with CTLs specific for heteroclitic peptides CYP239-19 and CYP239-139.

Fig. 10 is a graph showing the stability of HLA-A2/peptide complexes including the indicated peptides, as determined by TAP-deficient T2 cell assays.

Fig. 11 is a graph showing the stability of HLA-A2/peptide complexes including CYP190 and CYP528, as determined by TAP-deficient T2 cell assays.

Figs. 12A-12C are graphs showing that CYP190-specific CTL lyse peptide-pulsed T2 cells (A), HLA-A2⁺ myeloma cell lines, and HLA-A2⁺ primary ALL cells (C).

Figs. 13A and 13B are graphs showing that CYP190-specific CTL can be generated from cancer patients, such as a (A) prostate cancer patient (HLA-A2⁺), and (B) a multiple myeloma patient (HLA-A2⁺).

Fig. 14 is a graph showing the generation and verification of CYP1B1-specific tetramers including CYP239, CYP246, or a control, Tax 11.

Fig. 15 is a schematic representation of a system to detect CYP1B1 T cells by HLA-A2/peptide tetrameric complexes.

Fig. 16 is a set of graphs showing the detection of CYP1B1-specific CTL in normal HLA-A2⁺ donors.

Fig. 17 is a set of graphs showing the detection of CYP1B1-specific CTL in HLA-A2⁺ multiple myeloma patients.

Detailed Description

We have discovered that cytochrome P450 1B1 (CYP1B1) includes peptides that bind to HLA molecules. Antigen presenting cells (APCs) that present such peptides on their surfaces, in complexes with HLA, can activate

cytotoxic T lymphocytes (CTLs) to specifically lyse cells expressing CYP1B1, in an MHC-restricted fashion. The invention thus provides methods for immunotherapeutic targeting of CYP1B1-expressing cells, such as cancer cells, and methods of monitoring the efficacy of such therapeutic methods.

5 Based on our observations that CYP1B1 is a mediator of dioxin-related effects on tumorigenesis, in combination with searches of public literature databases, such as PubMed, we identified CYP1B1 as a potential universal tumor antigen. It is overexpressed in nearly 100% of human tumors (Murray *et al.*, Cancer Res. 57:3026-3031, 1997), whereas the expression in normal tissue is low
10 and limited to steroidogenic and steroid-responsive tissue (Buters *et al.*, Proc. Natl. Acad. Sci. USA 96:1977-1982, 1999). CYP1B1 is a member of the superfamily of monooxygenases responsible for the metabolic activation of environmental carcinogens. Mice lacking CYP1B1 have a much lower incidence of lymphoma than wild type mice after challenge with polycyclic aromatic
15 hydrocarbons, further implicating that CYP1B1 plays a role in oncogenesis.

T cell mediated anti-tumor immunity

As is noted above, there is considerable evidence that human T cells can specifically lyse tumor cells (Rosenberg, Immunity 10:281-287, 1999). Most
20 attention has been focused on CD8⁺ CTLs as the principle effector cells of antigen-specific anti-tumor immunity. Chief among the recent discoveries that have helped propel clinical efforts has been the characterization of tumor associated antigens (TAAs) (Boon *et al.*, Annual Review of Immunology 12:337-365, 1994). Pioneering studies in the early 1990s demonstrated the
25 existence of human TAAs using patients' CTLs that recognized peptides derived from these antigens (Van Pel *et al.*, Immunological Reviews 145:229-250, 1995; Rosenberg, Immunol. Today 18:175-182, 1997). Although these studies primarily focused on melanoma, TAAs have been subsequently characterized in several other malignancies (Van Pel *et al.*, Immunological Reviews 145:229-250,
30 1995; Rosenberg, Immunol. Today 18:175-182, 1997; Van den Eynde *et al.*, Curr. Opin. Immunol. 9:684-693, 1997), raising the hypothesis that most, if not all,

tumors express antigens that CTL can potentially attack. The demonstration that TAA-specific immune responses can lead to tumor regression has been borne out extensively in animal models (Rosenberg, Immunity 10:281-287, 1999).

Although the identification of TAAs using patients' CTLs has revitalized the field of T cell immunotherapy, these methods are slow, very expensive, and labor-intensive. Moreover, the strategy relies on the generation of tumor-specific T cell clones *in vitro*, suggesting that only a restricted set of TAAs will be identified by this method. With these limitations in mind, Pfreundschuh and colleagues developed an alternative approach, SEREX (serological identification of antigens by recombinant expression cloning), to identify TAAs (Sahin *et al.*, Curr. Opin. Immunol. 9:709-716, 1997). SEREX makes use of patients' antibody responses to tumor-derived genes and this strategy has accelerated the identification of TAAs significantly. Although several T cell-defined TAAs, such as the MAGE genes, have also been identified by SEREX, there is no information available about CTL epitopes for the vast majority of genes in the SEREX database, and, of course, such epitopes are required to activate a CTL response.

Although there is no doubt that the identification of numerous TAAs by CTL-based approaches or SEREX reflects the existence of an anti-tumor immune response, it remains to be determined if these antigens play a role as tumor regression antigens (Sarma *et al.*, J. Exp. Med. 189:811-820, 1999). As is mentioned above, most T cell epitopes in TAAs identified by patient CTLs have been demonstrated to be of low MHC binding affinity and/or low MHC/peptide complex stability. Clinical vaccination trials have circumvented this obstacle by utilizing altered peptides with higher MHC binding affinity and higher MHC/peptide complex stability (Rosenberg *et al.*, Nat. Med. 4:321-327, 1998). This quality distinguishes TAA-derived peptides from viral peptides that are almost exclusively of high binding affinity and high MHC/peptide complex stability (Feltkamp *et al.*, Mol. Immunol. 31:1391-1401, 1994; Sette *et al.*, J. Immunol. 153:5586-5592, 1994). The low binding affinity of TAA-derived peptides is likely to be one of the reasons why natural CTL responses against such peptides are not successful for tumor eradication. This is in agreement with the

finding that large numbers of TAA-specific CTLs co-exist with metastatic tumors in melanoma patients (Romero *et al.*, J. Exp. Med. 188:1641-1650, 1998). A recent study has even demonstrated that despite expansion, such CTLs were hyporesponsive, showing reduced cytotoxic and cytokine responses (Lee *et al.*,
5 Nat. Med. 5:677-685, 1999).

To overcome these limitations of currently known TAAs, we have developed methods to identify more universal TAAs, and, in particular, those containing T cell epitopes with high MHC binding affinity and high MHC/peptide complex stability. Such TAAs and MHC-binding peptides thereof can trigger
10 sufficient CTL responses against a broad range of tumor types. Rather than analyzing tumor-derived T cell clones or tumor-specific antibodies derived from patients, an alternative strategy was used, in which TAA and their CTL epitopes are deduced from genes known to be selectively expressed in tumors. By combining bioinformatics to predict peptides that bind to HLA with high affinity,
15 peptide binding analysis, and a powerful *in vitro* T cell expansion system, the cytochrome P450 1B1 (CYP1B1) was identified (see below). This TAA contains at least two peptide epitopes that (1) bind to HLA-A*0201 with high affinity and high MHC/peptide complex stability, (2) are naturally processed and presented by HLA-A*0201 molecules on the cell surface of a panel of tumor cell lines, (3)
20 elicit peptide-specific HLA-restricted CTL responses, and (4) are recognized by such CTL on a wide variety of different tumor histologies.

Deducing CTL epitopes in tumor associated antigens (TAAs): Making use of genomics and proteomics for tumor immunology

25 Current developments in genomics and proteomics suggest that numerous TAA candidate genes can be identified. The Human Genome Project (HGP), the Human Cancer Gene Anatomy Project (CGAP), the SEREX database, and other databases, including literature databases such as PubMed, provide an enormous set of data that can be analyzed to identify genes that fulfill the criteria
30 of universal tumor antigens, as are described above. It is clear that entering the post-genomic era, none of the classical approaches to characterize TAA, including

T cell cloning and testing of T cell clones against expression libraries (Boon *et al.*, Annual Review of Immunology 12:337-365, 1994), is suitable for the analysis of the ever-growing databases to identify a set of universal tumor antigens.

To overcome the limitations of prior methods in determining CTL epitopes, advances in bioinformatics can be applied. First, database mining and integration can be used to identify of universal tumor antigen candidates, which are genes that are expressed at a much higher level in tumor cells than in normal cells. Then, computational methods are used to predict peptides derived from these proteins for high-affinity binding to MHC molecules. The requirements for peptides to bind to class I HLA molecules and to elicit CTL responses have been studied extensively (Rammensee *et al.*, Annual Review of Immunology 11:213-244, 1993; Sidney *et al.*, Immunology Today 17:261-266, 1996). The strength of CD8⁺ CTL responses depends upon the binding affinity of the target peptide to MHC, the peptide-MHC complex stability, and the avidity of T cell receptor (TCR) binding for the peptide complex (Sette *et al.*, J. Immunol. 153:5586-5592, 1994; van der Burg *et al.*, J. Immunol. 156:3308-3314, 1996; Savage *et al.*, Immunity 10:485-492, 1999; Gallimore *et al.*, Eur. J. Immunol. 28:3301-3311, 1998). These factors directly influence the efficiency of peptide loading and the number of peptides expressed on the cell surface (Gallimore *et al.*, Eur. J. Immunol. 28:3301-3311, 1998). The vast majority of viral-derived immunodominant peptides are of high binding affinity and/or peptide-HLA complex stability (Feltkamp *et al.*, Mol. Immunol. 31:1391-1401, 1994; Sette *et al.*, J. Immunol. 153:5586-5592, 1994). Since only a very small portion of peptides can bind to MHC molecules, rapid and accurate methods to identify them, such as those used in the present invention, can expedite the search for CTL epitopes by orders of magnitude.

A great deal of effort has been expended on the development of computational methods to identify peptides that bind strongly to various MHC alleles. It began with the work of Rammensee and colleagues, who identified motifs in peptide sequences that serve as signatures of the MHC molecules to which they bind (Rammensee *et al.*, Immunogenetics 41:178-228, 1995). Motif-

based methods have recently been applied to the identification of CTL epitopes deduced from proteinase 3 (Molldrem *et al.*, Blood 88:2450-2457, 1996), MAGE-3 (Nijman *et al.*, Eur. J. Immunol. 23:1215-1219, 1993), MUC-1 (Brossart *et al.*, Blood 93:4309-4317, 1999), and telomerase (PCT/US99/25438).

5 Typically, only 20% of peptides that carry the motif bind to the respective MHC molecule. The inclusion of "secondary anchor" positions (Ruppert *et al.*, Cell 74:929-937, 1993), the so-called extended motif, significantly improves the specificity of motif-based methods, but they are available only for HLA-A*0201 (Ruppert *et al.*, Cell 74:929-937, 1993) and HLA-B*3501 (Schönbach *et al.*, J. Immunol. 154:5951-5958, 1995).

10 Many other statistically-based computational methods have been developed (for reviews, see, *e.g.*, Hammer, Curr. Opin. Immunol. 7:263-269, 1995; Parker *et al.*, Immunol. Res. 14:34-57, 1995), including the polynomial method (Gulukota *et al.*, J. Mol. Biol. 267:1258-1267, 1997), methods based on neural nets (Gulukota *et al.*, J. Mol. Biol. 267:1258-1267, 1997; Brusic *et al.*, Bioinformatics 14:121-130, 1998; Brusic *et al.*, Nucleic Acids Res. 26:368-371, 1998), a method that assigns a score for each amino acid at each position as determined experimentally *via* single residue substitutions (Hammer *et al.*, J. Exp. Med. 180:2353-2358, 1994), and a method developed by Parker *et al.* based on a database of the half-lives of bound

20 β 2-microglobulin (β 2m) in MHC-peptide complexes (Parker *et al.*, J. Immunol. 152:163-175, 1994). The method developed by Parker *et al.* assumes that the dissociation of β 2m is rate-limited by the dissociation of peptide, so that variation in the microglobulin half-life reflects variation in the peptide half-life. The variation is, in turn, assumed to reflect the variation in the binding affinity of the peptide. A weight matrix is then determined to best reflect the half-lives,

25 assuming that the contribution of one peptide position does not depend on its neighboring positions.

Weng and colleagues have recently developed a new statistical method (implemented as a computer program named LPpеп; Weng *et al.*, <http://bioinformatics.bu.edu/peptides.html>) to predict strong

30 HLA-A*0201-binding peptides. It determines the contributions for each of the 20

amino acids at each of the positions of a peptide using a linear programming algorithm. When tested on a data set of over 1000 peptides having known binding affinities, LPpep has a higher sensitivity (>0.75) and specificity (>0.9) than four other available methods.

5

High volume analysis of peptide MHC affinity and MHC/peptide complex stability

The basic principles of peptide binding to MHC molecules have been well established in the field (Rammensee *et al.*, Annual Review of Immunology 11:213-244, 1993; Rothbard *et al.*, Annual Review of Immunology 9:527-565, 1991; Engelhard, Annual Review of Immunology 12:181-207, 1994; Madden, Annual Review of Immunology 13:587-622, 1995; Pamer *et al.*, Annual Review of Immunology 16:323-358, 1998; Rock *et al.*, Annual Review of Immunology 17:739-779, 1999), and numerous assay systems have been developed to analyze the binding of any given peptide to MHC molecules. Binding has been analyzed using intact TAP-deficient cells (Salter *et al.*, EMBO J. 5:943-949, 1986; Schumacher *et al.*, Cell 62:563-567, 1990) and by *in vitro* assays utilizing purified HLA molecules (Ruppert *et al.*, Cell 74:929-937, 1993; Schumacher *et al.*, Cell 62:563-567, 1990; Townsend *et al.*, Cell 62:285-295, 1990). While most assay systems have focused on the maximal binding affinity, it has recently been suggested that the dissociation rate of MHC and peptide (also measured as MHC/peptide complex stability) may be a more important determinant for characterizing a peptide as a dominant T cell epitope (van der Burg *et al.*, J. Immunol. 156:3308-3314, 1996; Busch *et al.*, J. Immunol. 160:4441-4448, 1998; Kammer *et al.*, J. Exp. Med. 190:169-176, 1999).

25

In vitro analysis of CTL responses

The generation of antigen-specific T cells *in vitro* is a classical immunological technique. Antigen-specific T cells can be generated relatively easily if the peptides used to make such cells are: (1) immunodominant, (2) of viral or other non-self origin, (3) expressed at a reasonably high copy number on the cell surface (Porgador *et al.*, Immunity 6:715-726, 1997), and (4) of high

affinity for, and of low dissociation rate (high MHC/peptide complex stability) from, MHC, and if the T cell pool under study has been exposed to the antigen *in vivo* prior to *ex vivo* analysis (recall response). The frequency analysis of peptide-specific T cells by tetramer technology (see below) revealed a
5 significantly higher frequency than earlier assays based on *in vitro* expansion had suggested.

It is therefore apparent that only a fraction of specific CTLs are expanded in classical *in vitro* systems utilizing unstimulated peripheral blood mononuclear cells (PBMC) as antigen presenting cells (McMichael *et al.*, J. Exp. Med. 187:1367-1371, 1998). To circumvent these pitfalls, *in vivo* systems
10 utilizing transgenic mice carrying human HLA genes have been introduced (Man *et al.*, International Immunology 7:597-605, 1995; Wentworth *et al.*, International Immunology 8:651-659, 1996; Alexander *et al.*, J. Immunol. 159:4753-4761, 1997). However, these systems are expensive and are not suitable for screening
15 multiple peptide epitopes simultaneously. Making use of new findings in basic immunology, it is possible to optimize further currently available *in vitro* culture technology. The use of an APC instead of PBMC as stimulators is only one example.

We have developed a system that utilizes dendritic cells (DC) for
20 primary activation and CD40-activated B cells (CD40-B) for re-stimulation, thereby mimicking the physiological sequence of events between T cells and APCs during an ongoing immune response (Schultze *et al.*, J. Exp. Med. 89:1-12, 1999; Schultze *et al.*, J. Clin. Invest. 100:2757-2765, 1997). This system has been successfully used for the identification of T cell epitopes derived from hTERT
25 and the clonal immunoglobulin in B cell malignancies (PCT/US99/25438). From a single blood draw, professional APCs, including DCs and CD40-activated B cells, are generated, and the remaining PBMCs are enriched for CD8⁺ T cells. T cells are primarily stimulated with peptide-pulsed DC, and repeatedly stimulated with peptide-pulsed CD40-B cells. Peptide-specificity and HLA-restriction is
30 analyzed after a total of 2-5 stimulations, depending on the antigen under study. This system is not only very powerful in amplifying rare T cells against

TAA-derived peptides, but has several other advantages: (1) it is relatively cheap compared to transgenic mice, (2) a single blood draw is sufficient to generate all cellular components necessary, and (3) the use of professional APCs for restimulation is superior to PBMC.

Classically, the function of CTLs *in vitro* has been defined by cytotoxicity assays using radioactive chromium. Clearly, cytotoxicity analysis is an important component of the characterization of a novel TAA, since tumor cell lysis is the ultimate goal of any TAA-directed immunotherapeutic intervention. However, such assays are not suitable to determine the frequency of peptide-specific CTLs. In addition, the sensitivity of cytotoxicity assays to identify very small numbers of specific CTLs is insufficient. To detect very low numbers of specific CTLs and to determine their frequency, two new technologies, namely the tetramer technology (Altman *et al.*, Science 274:94-96, 1996) and cytokine ELISPOT analysis (Herr *et al.*, J. Immunol. Methods 203:141-152, 1997), have been developed and applied to tumor immunology. In particular, tetramers have been suggested as a tool to enrich CTL lines for peptide-specific CTL (Dunbar *et al.*, Curr. Biol. 8:413-416, 1998; Yee *et al.*, J. Immunol. 162:2227-2234, 1999; Valmori *et al.*, Cancer Res. 59:2167-2173, 1999). Currently, the tetramer technology is still technically demanding and it is not possible to generate numerous tetramers in small quantities to screen peptide-specific CTL responses against a larger set of unknown peptides. For this purpose, cytokine ELISPOT is more suitable (Herr *et al.*, J. Immunol. Methods 203:141-152, 1997).

Experimental Results

The dioxin-inducible cytochrome P450 1B1 (CYP1B1)

Using the methods described above (also see PCT/US99/25438), we identified the dioxin-inducible cytochrome P450 1B1 (CYP1B1) as a potential TAA. A list of peptides predicted to bind to all HLA alleles available are listed in the Sequence Appendix. The prediction was carried out using three different algorithms that are freely available on the Internet:

<http://engpub1.bu.edu/LPpep-cgi/peptide2.cgi>

<http://www.uni-tuebingen.de/uni/kxi/>

http://bimas.dcrtnih.gov/molbio/hla_bind/

Analysis of the CYP1B1 sequence by two independent prediction algorithms
5 (BIMAS and LPpep, see Experimental Methods, below) revealed two peptides
(CYP239 and CYP246) predicted to bind to HLA-A*0201, the most common
HLA allele (Table 1). These peptide sequences are unique in the public gene
databases and in particular are not found within any other member of the
cytochrome P450 family. (Also see below for additional CYP1B1 peptides (*e.g.*,
10 CYP190 and CYP528) identified according to the invention.)

Peptide binding of CYP1B1 derived peptides

Binding of both peptides to HLA-A2, as well as their complex stability,
was determined using a cellular assay employing TAP-deficient T2 cells (Table 1;
15 PCT/US99/25438). Both peptides stabilized HLA-A2 molecules on the surface of
T2 cells to a similar extent as a positive control peptide (F271) derived from the
tumor antigen MAGE-3 (Nijman *et al.*, Eur. J. Immunol. 23:1215-1219,1993),
which is known to bind HLA-A2 with high affinity. In particular, T2 cells were
incubated with peptide in serum-free medium for up to 18 hours, harvested,
20 washed, and subsequently stained with FITC-labeled anti-HLA-A2 mAb BB7.2
(maximum peptide binding). Increase in fluorescence intensity was determined as
a function of peptide binding. For analysis of complex stability, T2 cells were
cultured in serum-free media for an additional 2, 4, 6, or 24 hours, and
subsequently analyzed for HLA-A2 expression by flow cytometry. As is shown
25 in Fig. 1, the MAGE-3-derived peptide, which induces CTL responses in the
majority of all normal donors, demonstrated high binding affinity and complex
stability. Although both CYP1B1-derived peptides bound to HLA-A2, CYP246
showed a significantly lower complex stability than CYP239 and MAGE-3.
Moreover, attempts to induce CTL responses were successful in 13/15 donors
30 against CYP239, but only 4/9 donors for CYP246. Our data further show that

complex stability might be a more important factor than binding affinity for the likelihood to generate peptide-specific CTL responses.

TABLE 1

Binding of CYP1B1 and control peptides to human HLA-A*0201

sequence	BIMAS ¹	LPpep ²	binding affinity ³ [FI]
SLVDVMPWL	1108	2.88	3.8
WLQYFPNPV	1216	6.23	3.4
FLWGPRALV	2655	7.63	3.2

1 Peptide prediction at BIMAS (Bioinformatics & Molecular Analysis Section): scores for predicted binding are calculated as half-life of MHC/peptide complexes (peptides with scores > 500 were chosen as potential candidates).

2 LPpep (peptide prediction at Boston University): scores are predicted as arbitrary $\ln(IC_{50})$ concentrations (peptides with scores < 7 were chosen as potential candidates).

3 Mean fluorescence with peptide / mean fluorescence without peptide - 1. Results representative of 4 experiments.

Peptide-specific killing

To test whether CYP239 and CYP246 reactive T cells are present in the human T cell repertoire, CTL lines were generated *ex vivo* by repetitive stimulation with peptide pulsed autologous APC. CTL specific for CYP239 were induced from peripheral blood mononuclear cells (PBMC) in 11 of 13 healthy HLA-A2⁺ donors (Fig. 2A). These CTL specifically lysed T2 cells pulsed with CYP239 peptide, while no cytotoxicity occurred against unpulsed T2 cells or T2 cells pulsed with the F271 peptide from MAGE-3. CYP246 specific CTL were generated in 4 of 10 healthy HLA-A*0201⁺ donors (Fig. 2B). HLA-A2 restriction was demonstrated using autologous and HLA-A2 mismatched CD40-activated B cells (CD40-B) as targets (Figs. 2C and 2D). CYP239-specific CTL lysed autologous CD40-B pulsed with CYP239, but not allogeneic HLA-A2- CD40-B pulsed with CYP239 (Fig. 2C). Similar results were obtained for CYP246-specific CTL (Fig. 2D).

Experiments titrating the concentration of peptide onto the CD40-activated B cells before the cytotoxicity assay further support the peptide-specificity of the CTL generated against the CYP239 peptide. Comparing the data with published data in the literature the cell line tested in this experiment is of intermediate avidity. Alternatively, the cell line contains both high and low avidity CTL and the curve represents the sum of the actions of these CTLs (Fig. 3).

For both CYP239 and CYP246 CTL, specificity was further demonstrated using peptide/MHC tetramers (Fig. 2E). Frequency analysis using CYP239 tetramers demonstrated that 1.4-2.4% of all CD8⁺ T cells recognized the CYP239 peptide, a percentage comparable to previously published data for gp100 specific (Yee *et al.*, J. Immunol. 162:2227-2234, 1999) or proteinase-3 specific CTL lines (Molldrem *et al.*, Cancer Res. 59:2675-2681, 1999). CYP246-specific CTLs were detected with CYP246 tetramer, but the frequency of specific CTL was lower (0.47%). To further confirm peptide-specific cytotoxicity, CYP239 tetramer-positive CTL were sorted and expanded using phytohemagglutinin (PHA), IL-7, IL-2, and irradiated allogeneic PBMC. These CTL lysed T2 cells pulsed with CYP239 at extremely low E:T ratios, but not unpulsed T2 cells or T2 cells pulsed with an irrelevant HLA-A2 binding peptide (Fig. 2F). Thus, CYP1B1 contains at least two HLA-A*0201 binding peptides, and T cells recognizing these peptides are present in the T cell repertoire of healthy donors.

CYP1B1 specific CTL lyse CYP1B1 expressing tumors in an HLA-A2 restricted fashion

Although peptide-specificity of CTL is demonstrated by lysis of peptide-pulsed target cells, it is important to show that tumor cells themselves process and present the peptide in the groove of their MHC molecules (Yee *et al.*, J. Immunol. 162:2227-2234, 1999). We approached this question by using a panel of HLA-A2⁺ and HLA-A2⁻ tumor cell lines that all express CYP1B1 protein. CYP239- and CYP246-specific CTL from healthy donors were then screened for cytotoxicity (Figs. 4A-4H). CYP239 CTL (Fig. 4A) and CYP246 CTL (Fig. 4B) showed

specific lysis of HLA-A2⁺ melanoma cell line K029, but not HLA-A2⁻ SK-MEL-2 cells. Similarly, the HLA-A2⁺ myeloma cell lines IM-9 and U266 were lysed by CYP239 CTL (Fig. 4C) and CYP246 CTL (Fig. 4D), while the HLA-A2⁻ myeloma HS-Sultan cell line was not killed. Finally, specific cytotoxicity by CYP239 CTL (Fig. 4E) and CYP246 CTL (Fig. 4F) was observed against the HLA-A2⁺ ovarian carcinoma cell line 36M, but not the HLA-A2⁻ line SK-OV-3. These data show that CYP1B1 derived peptides are naturally processed and presented by tumor cell lines of different tissue origin.

Since CYP1B1 expression has been reported in fibroblasts (Eltom *et al.*, Carcinogenesis 19:1437-1444, 1998) and monocytes (Baron *et al.*, Biochem. Pharmacol. 56:1105-1110, 1998), we analyzed an HLA-A2⁺ fibroblast cell line (GM847) and primary peripheral blood derived monocytes from four healthy donors as targets for CYP1B1-specific CTL. Western blot analysis showed that of these normal cells express low or absent levels of CYP1B1. As is shown in Figs. 4G and 4H, CYP239 and CYP246-specific CTL failed to lyse these normal targets. In contrast, CD40-activated B cells strongly express CYP1B1 protein (detected by Western blot), but these normal cells were not lysed by CYP239- or CYP246-specific CTL (Figs. 2C and 2D), suggesting that there is a differential expression of CYP1B peptides on tumor cells.

Methods to improve killing of tumor cell lines

The experiments described so far suggest that CYP239 peptide is most likely expressed at low levels on tumor cell MHC. Alternatively, tumor cells could be more resistant to CTL-mediated lysis. To address these issues and to determine whether the increase of peptide on the cell surface of tumor cells would lead to increase killing of the tumor cells, tumor cells were pulsed with the specific peptide before they were used in chromium release assays. We could demonstrate that peptide-pulsing of tumor cells significantly increased killing of the target cells, suggesting that the level of naturally expressed CYP239 peptide is low on the tumor cells, however, that these cells can be readily killed once the level of peptide is increased. This also suggests that any methodology to increase

the expression of CYP1B1-derived peptides on the cell surface will make the tumor cell a susceptible target for CYP1B1-specific CTLs (Fig. 5).

Lysis of primary HLA-A2⁺ follicular lymphoma cells

5 CYP1B1-specific CTLs were then evaluated for cytotoxicity against primary tumor tissue. Because CYP1B1^{-/-} mice demonstrate a significantly reduced incidence in carcinogen-induced lymphomas (Buters *et al.*, Proc. Natl. Acad. Sci. U.S.A. 96:1977-1982, 1999), we chose to study human primary follicular lymphoma (FL) as a model tumor target for CYP1B1 specific CTL.

10 Tumor cells from two HLA-A2⁺ FL samples and one HLA-A2⁻ FL sample were found to be CYP1B1⁺ as assessed by Western blot analysis. Using these target cells, we found that CTL lines generated against CYP239 or CYP246 were cytotoxic for the HLA-A2⁺ FL, while no killing of the HLA-A2⁻ FL was observed (Figs. 6A and 6B). We also demonstrated lysis of HLA-A2⁺ primary acute

15 myeloid leukemia (AML) cells, but not HLA-A2⁻ primary AML cells by CYP239 CTL (Fig. 6C). These data show that both CYP1B1-derived peptides are processed and presented by HLA-A2 on primary tumor cells and that HLA-A2 restricted CYP1B1 specific CTL from healthy donors can recognize and kill these target cells.

20 *Generation of CYP1B1-specific CTL from patients with multiple myeloma*

Similar to experiments described for healthy donors, we next attempted to generate CYP1B1-specific CTL from peripheral blood of cancer patients. HLA-A2⁺ patients with multiple myeloma (n=3) or follicular lymphoma (n=1)

25 (Table 2) were tested for *ex vivo* generation of CYP239 (n=4) or CYP246 (n=2) specific CTL. Generation of all cellular components of our *ex vivo* system (*i.e.*, dendritic cells, CD40-B, and CTL), as well as expansion of CTL to CYP239 and CYP246 were similar to results obtained for healthy donors. Using peptide-pulsed T2 cells as targets, we demonstrated CYP239-specific CTL in all four

30 patients (Fig. 7A). Due to lower numbers of PBMC available, CYP246-specific CTL cultures were only initiated in patients 3 and 4. CYP246-specific CTLs were

detected in both patients. These patient-derived lines showed tumor-specific lysis of HLA-A2⁺ myeloma cell lines U266 and IM-9, but not the HLA-A2⁻ myeloma cell line HS-Sultan (Fig. 7B). Because autologous tumor cells were not available from these patients, we tested the same FL samples described above as primary tumor targets. CYP239-specific CTL from patient 1 lysed both HLA-A2⁺ FL samples but not the HLA-A2⁻ (18% vs. 0% at an E:T ration of 30:1).

TABLE 2

patient	age	sex	disease	stage	prior treatment	CTL induction	
						CYP239	CYP246
1	41	f	Multiple Myeloma	I A	none	yes	ND
2	47	f	Multiple Myeloma	II A	none	yes	ND
3	40	m	Multiple Myeloma	III A	High-Dose Dexamethasone, discontinued >30d prior to leukapheresis	yes	yes
4	29	m	Non Hodgkin's Lymphoma (Follicular Lymphoma)	III A	none	yes	yes

Patient characteristics, prior treatment, and CTL induction

ND = not determined

10

Combining CYP1B1- and hTERT-specific CTL

We next analyzed the combination of CYP1B1-specific CTL with hTERT-specific CTL (Vonderheide *et al.*, Immunity 10:673-679, 1999). To
 15 normalize for equal susceptibility to T-cell mediated lysis, we used a mixture (1:1 ratio) of T2 cells pulsed with either CYP239 or I540 hTERT peptide (Vonderheide *et al.*, Immunity 10:673-679, 1999) as a model for heterogeneous antigen expression. Equal ⁵¹Cr labeling of both T2 cell populations was assured. Under these conditions, it is expected that either CTL line alone can only lyse a
 20 maximum of 50% of the target cell population while the combination if effective has the potential to kill >50% of all cells (Janeway, *Immunobiology: The Immune System in Health and Disease* (Garland Publishing c/o Taylor & Francis, Inc.,

New York, 1999), p. 297). This is true for specific lysis regardless of the E:T ratio used. As postulated, the combination of CYP239- and I540-specific CTL was superior to each CTL line alone, achieving specific lysis of >50% (Fig. 8). Similar observations were made in independent experiments using CTL generated from two different donors. We also analyzed the effect of combined CYP1B1 and hTERT CTL on the HLA-A2⁺ tumor cell line IM-9, which expresses both antigens. In two experiments, we observed additive lysis of CYP239- and I540-specific CTL across a range of E:T ratios. These data demonstrate the potential of enhancing antigen-specific T cell immunity by targeting multiple antigens, such as CYP1B1 and hTERT.

Use of heteroclitic peptides

To improve immunogenicity of CYP1B1 derived peptides, we designed heteroclitic peptides optimized for binding affinity to MHC. We have already shown that CTL generated against the CYP239 wild type peptide can recognize and lyse target cells pulsed with the heteroclitic peptide CYP239-19 equally well, while CTL generated with CYP239 do not recognize CYP239-139. These data show that despite similar binding, the change of a third amino acid does not allow for recognition by CTL specific for CYP239. Most likely, the amino acid change induced a change in the three dimensional structure of the peptide not allowing TCR activation (Fig. 9). To design heteroclitic peptides with higher binding affinity, we used an algorithm available on the Internet (<http://engpub1.bu.edu/LPpep-cgi/peptide3.cgi>). Two heteroclitic peptides to the immunogenic peptide CYP239 have been designed as examples to improve binding affinity, complex stability, and, potentially, immunogenicity (Table 3).

TABLE 3

Examples of Heteroclitic Peptides Optimized for Binding to HLA-A*0201

heteroclitic 9mers

position	peptide	nmer	Parker score	Zhiping score	T2 assay result
292	YLYAFILSV	9	8948.1	-0.99	n.d.
344	YLYTRYPDV	9	1535.7	0.7	n.d.
380	YLYAFLYEV	9	8948.1	-3.51	n.d.
246	YLYYFPNPV	9	3890.5	-0.27	n.d.
239 (1, 3, 9)	YLYDVMPWV	9	53099.7	-3.42	2.00
239 (1, 9)	YLVDVMPWV	9	16593.6	-0.85	2.16
239 (1, 3)	YLYDVMPWL	9	16309.2	-1.76	n.d.
239 (3, 9)	SLYDVMPWV	9	11543.4	-1.35	n.d.
239 (1)	YLVDVMPWL	9	5096.6	0.81	n.d.
239 (9)	SLVDVMPWV	9	3607.3	1.22	n.d.
239 (3)	SLYDVMPWL	9	3545.5	0.31	n.d.

5

Peptide binding of heteroclitic CYP239 peptides

The T2 assay described above was used to determine binding and dissociation rate of heteroclitic peptides engineered for optimal binding to HLA molecules. Two heteroclitic peptides to CYP239 were tested and shown to have higher peptide/MHC-complex stabilities, as is shown in Table 4. While the control peptide MAGE-3 and the CYP239 peptide showed no significant binding at 24 hours (0.14 resp. 0.12), both heteroclitic peptides still bound to HLA-A*0201 (0.72 resp. 0.73).

15

TABLE 4**Examples of heteroclitic peptides optimized for binding to HLA-A*0201**

time post-pulsing [hours]		0	2	4	6	
MAGE-3	FLWGPRLV	1.88	1.41	0.93	0.77	0.14
CYP239	SLVDVMPWL	1.91	1.37	0.78	0.58	0.12
CYP239-19	YLVDVMPWV	2.16	1.57	1.31	1.13	0.72
CYP239-139	YLYDVMPWV	2.00	1.51	1.24	1.16	0.73

The following Tables 5 and 6 show predicted mutations to improve HLA-A2
5 binding of CYP1B1 239 and CYP1B1 246.

TABLE 5
Predict Mutations to Improve HLA-A2 Binding CYP239

- 5 Under each position, a list of possible amino acid mutations is given, followed by the change in the predicted $\ln(\text{IC}_{50})$ produced by the mutation with respect to the original peptide's score.

POSITION								
1	2	3	4	5	6	7	8	9
K (0.17)	*	A (1.31)						A (0.60)
M (2.03)		C (1.35)						I (1.36)
F (0.60)		G (0.57)						V (1.66)
Y (2.07)		H (0.78)						
		L (1.63)						
		M (2.00)						
		F (1.40)						
		P (0.19)						
		S (0.55)						
		W (1.38)						
		Y (2.57)						

* indicates best amino acid is already present

Original peptide: SLVDVMPWL, predicted $\ln(\text{IC}_{50}) = 2.88$

10 **Top scoring peptide under given constraints: YLYDVMPWV, predicted $\ln(\text{IC}_{50}) = -3.42$**

TABLE 6
Predict Mutations to Improve HLA-A2 Binding CYP246

5 Under each position, a list of possible amino acid mutations is given, followed by the change in the predicted $\ln(\text{IC}_{50})$ produced by the mutation with respect to the original peptide's score.

POSITION								
1	2	3	4	5	6	7	8	9
A (1.53)	*	A (1.50)						*
R (1.08)		D (0.10)						
N (0.33)		C (1.54)						
C (0.88)		G (0.76)						
G (1.39)		H (0.97)						
L (0.92)		I (0.16)						
K (1.84)		L (1.82)						
M (3.70)		M (2.19)						
F (2.27)		F (1.59)						
S (1.67)		P (0.38)						
T (0.94)		S (0.74)						
Y (3.74)		W (1.57)						
V (1.21)		Y (2.76)						
		V (0.19)						

* indicates best amino acid is already present

Original peptide: WLQYFPNPV, predicted $\ln(\text{IC}_{50}) = 6.23$

Top scoring peptide under given constraints: YLYYFPNPV, predicted $\ln(\text{IC}_{50}) = -0.27$

10

Identification of additional HLA-A2 binding epitopes from CYP1B1

Binding studies were carried out to characterize additional CYP1B1-derived peptides that are predicted to bind to HLA-A2. Table 7, below, shows the sequences of additional peptides that are predicted to bind to HLA-A2.

15

TABLE 7

Predicted binding of epitopes to HLA-A2

Nonamers predicted to bind to HLA-A*0201

position	peptide	Parker		LPep		SYFPEITHI	
		score	rank	score	rank	score	rank
25	LLLSVLATV	1006	3	3.54	4	32	1
88	RLGSCPIVV	29	18	4.61	6	20	31
190	FLDPRPLTV	128	11	6.52	15	26	5
239	SLVDVMPWL	1108	2	2.88	2	24	9
246	WLQYFPNPV	1216	1	6.23	12	21	22
292	MMDAFILSA	21	19	3.31	3	20	29
344	LLFTRYPDV	656	4	4.69	7	24	7
377	NLPYVLAFL	270	8	7.1	21	25	6
380	YVLAFLYEA	65	14	1.56	1	20	27
479	QLFLFISIL	283	6	5.66	9	26	4
528	LLDSAVQNL	33	16	4.08	5	26	3

Table 1a

Decamers predicted to bind to HLA-A*0201

position	peptide	Parker		LPep		SYFPEITHI	
		score	rank	score	rank	score	rank
24	LLLSVLATV	1006	1	4.55	5	24	1
88	RLGSCPIVL	20	22	3.08	2	26	3
343	LLFTRYPDV	656	2	5.6	9	343	7
477	KMQLFLFISI	50	13	1.29	1	19	31
479	QLFLFISILA	18	24	3.86	3	15	67
486	ILAHQCDFRA	49	14	3.87	4	18	36

Table 1b

5

Peptides were pulsed onto TAP-deficient T2 cells, and the maximum binding and the stability over time were assessed by flow cytometry. As is shown in Fig. 10, CYP190 and CYP528 show the longest half-life on the cell surface. Additional experiments were carried out to characterize these peptides, in particular, CYP190. As is shown in Fig. 11, further binding studies using TAP-deficient T2 cells showed that CYP190/A2 complexes can be detected as long as 24 hours after peptide withdrawal. Moreover, as is shown in Figs. 12A-12C, CYP190-specific CTL can be generated from normal HLA-A2⁺ donors, and these CTL can lyse peptide-pulsed T2 cells (Fig. 12A), HLA-A2⁺ myeloma cell lines (Fig. 12B), and HLA-A2⁺ primary ALL cells (Fig. 12C). In addition, as is shown

15

in Figs. 13A and 13B, CYP190-specific CTL can be generated from HLA-A2⁺ cancer patients (Fig. 13A, prostate cancer patient, and Fig. 13B, multiple myeloma patient), and show specific lysis.

We also identified HLA-A3 binding epitopes from CYP1B1. Using the BIMAS server, for example, we identified the peptides shown in Table 8, in which the positive control is a peptide derived from influenza A.

TABLE 8
Peptides predicted to bind to HLA-A3 (BIMAS server)

10

rank	position	sequence	score
10mers			
1	508	GLTIKPKSFK	90
2	445	FLDKDGLINK	60
3	450	GLINKDLTSR	27
9mers			
1	150	SMMRNFFTR	54
2	408	SVLGYHIPK	27
positive control	NP265	ILRGsvAHK	90

As is shown in Table 9, these peptides were tested in a binding assay to T2 cells transfected with HLA-A3 (NP265= positive control from influenza A). These studies showed that CYP408, CYP445, and CYP150, which are not homologous to other cytochrome P450 isoenzymes, repeatedly bound to HLA-A3.

TABLE 9

Binding assay of peptides to T2 cells transfected with HLA-A3

peptide	FI class I	FI
PBS	15.3	
NP265	19.4	0.27
CYP508	16.4	0.07
CYP408	16.9	0.10
CYP445	19.5	0.27
CYP450	16.8	0.10
CYP150	17.2	0.12
Flu-MP58	34.8	1.27

5

In further studies, we detected CYP1B1 reactive T cells in HLA-A2+ normal donors HLA-A2+ cancer patients (Fig. 14). Specific binding of tetramers with CYP239 and CYP246 peptides was confirmed on T cell lines generated
 10 against the respective peptide. No binding could be detected on T cells generated against an irrelevant peptide. A tetramer containing a peptide from HTLV was used as a negative control.

We also devised a system for detecting CYP1B1-specific T cells by HLA-A2/peptide tetrameric complexes, as is illustrated in Fig. 15. CD8⁺
 15 T cells from normal HLA-A2⁺ myeloma patients (n=10) were isolated and analyzed with HLA-A2/peptide tetrameric complexes directly *ex vivo* and after a 10 day *in vitro* restimulation period with peptide, cytokines, and irradiated PBMC. Viral peptides were used as positive (influenza A, EBV) and negative (HTLV Tax) controls.

20 As is shown in Fig. 16, T cells from HLA-A2+ healthy donors (n=8) were stained with CYP239 and CYP246 tetramers directly *ex vivo* and 10 days after *in vitro* restimulation with CYP239 or CYP246 peptides. The level of detection on day 10 is at 0.05% as determined from background staining of HLA-A2⁻ donors. No expansion of CYP239-specific T cells was detected in healthy donors on day
 25 10 (mean 0.022%±0.018%). CYP246-specific T cells were detected in 2 healthy donors with one rising to 0.5% (mean 0.032%±0.022%).

As is shown in Fig. 17, T cells from HLA-A2+ multiple myeloma patients (n=10) were stained with CYP239 and CYP246 tetramers directly *ex vivo* and 10 days after *in vitro* restimulation with CYP239 or CYP246 peptides. The level of detection on day 10 is at 0.05% as determined from background staining of HLA-A2- donors. 4 patients showed T cells reactive against CYP239 >0.05% on day 10 (mean 0.068%±0.055%), whereas 5 patients showed reactivity against CYP246 (mean 0.098%±0.080%).

Table 10 shows the sequence of CYP1B1 and the sequences of CYP1B1 peptides that were identified by LPEP analysis as having binding affinity for HLA-A2.

TABLE 10
Identify HLA-A2 Binding Peptide Fragments. CYP1B1

Input Sequence:

5

MGTSLSPNDPWPLNPLSIQQTLLLLLSVLATVHVVGQRLLRQRRRQLRSAPPGPFAWPLIGNAAA

VGQAAHLSFARLARRYGDVFQIRLGSCPIVVNLGERAIHQALVQQGSAFADRPASFRVVSNGGR

SMAFGHYSEHWKVQRRAAHSMNRNFFTRQPRSRQVLEGHVLSARELVALLVRGSADGAFLDP

RPLTVVAVANVMSAVCFGCRYSHDDPEFRELLSHNEEFGRTVGAGSLVDVMPWLQYFPNPVRTV

10

TITDIFGASQDTLSTALQWLLLLFTRYPDVQTRVQAEQVVGDRDLPCMAGDQPNLPYVLAFLYE

AMRFSSFPVPTIPHATTANTSVLGYHIPKDTVVFVNQWSVNHDPKWPENFDPAFLDKDGLI

NKDLTSRVMIFSVGKRRRCIGEELSKMQLFLFISILAHQCDFRANPNEPAKMNFSYGLTIKPKSFKVN

VTLRESMELLDASVQNLQAKETCQ

15

Listed below are 9-residue peptides predicted to bind to the HLA-A2 allele with a $\ln(\text{IC}_{50}) < 8$. The first entry represents the location in the original sequence of the first amino acid of that peptide. Following the location is the peptide, for which the predicted $\ln(\text{IC}_{50})$ is given as the third entry.

20

22

TLLLLLSVL

7.08

23

LLLLLSVLA

7.71

24

LLLLSVLAT

6.05

25

LLSVLATV

3.54

55

FAWPLIGNA

5.11

88

RLGSCPIVV

4.61

25

95

VVLNGERAI

6.58

190

FLDPRPLTV

6.52

200

AVANVMSAV

6.14

239

SLVDVMPWL

2.88

246

WLQYFPNPV

6.23

30

292

MMDAFILSA

3.31

312

GARLDLENV

7.87

314

RLDLENVPA

6.27

322

ATITDIFGA

6.74

334

TLSTALQWL

6.64

35

344

LLFTRYPDV

4.69

377

NLPYVLAFL

7.10

380

YVLAFLYEA

1.56

381

VLAFLYEA

6.09

394

FVPVTIPHA

7.03

40

419

VVFVNQWSV

7.35

479

QLFLFISIL

5.66

487

LAHQCDFRA

7.54

510

TIKPKSFKV

7.60

45

528

LLDSAVQNL

4.08

Listed below are 10-residue peptides predicted to bind to the HLA-A2 allele with a $\ln(\text{IC}_{50}) < 8$.

	4	SLSPNDPWPL 5.26
	20	QTLLLLLSV 6.75
50	21	TLLLLLSVL 7.01
	22	TLLLLSVLA 5.18
	23	LLLLSVLAT 7.36
	24	LLLLSVLATV 4.55
	26	LLSVLATVHV 5.86
55	88	RLGSCPIVV 3.08
	190	FLDPRPLTVV 7.88
	199	VAVANVMSAV 7.87
	234	TVGAGSLVDV 7.73

255 RTVFREFEQL 7.72
 334 TLSTALQWLL 5.85
 336 STALQWLLLL 5.96
 343 LLLFTRYPDV 5.60
 5 380 YVLAFLYEAM 5.54
 388 AMRFSSFVPV 7.39
 418 TVVFVNQWSV 6.72
 477 KMQLFLFISI 1.29
 479 QLFLFISILA 3.86
 10 486 ILAHQCDFRA 3.87
 494 RANPNEPAKM 7.06
 502 KMNFSYGLTI 7.12

15 The following Experimental Methods were used to obtain some of the Experimental Results set forth above.

Experimental Methods

Donor and Patient Samples

20 Peripheral blood from healthy blood donors and cancer patients (Table 2) was obtained by leukapheresis and peripheral blood mononuclear cells (PBMC) were purified by Ficoll-density centrifugation (Schultze *et al.*, J. Clin. Invest. 100:2757-2765, 1997). Primary NHL and AML samples were obtained from discarded specimens. Leukapheresis products and tumor tissue were obtained
 25 following informal consent and approval by our institute's Review Board.

Cell Lines

The melanoma cell line K029 was a kind gift of Dr. G. Dranoff (Dana-Farber Cancer Institute, Boston). The fibroblast cell line GM847 was a kind gift
 30 of Dr. W. Hahn (Whitehead Institute of Biomedical Research, Cambridge). The 36M ovarian carcinoma cell line was a kind gift of Dr. S. Cannistra (Beth Israel Deaconess Hospital, Boston). The TAP-deficient T2 cell line; the multiple myeloma cell lines U266, IM9, and HS-Sultan; the melanoma cell line SK-MEL-2; and the ovarian carcinoma cell line SK-OV-3 were obtained from the American
 35 Type Culture Collection (ATCC; Manassas, VA).

Peptides

The peptides CYP239 (SLVDVMPWL; SEQ ID NO:1) and CYP246 (WLQYFPNPV; SEQ ID NO:2) from CYP1B1, the I540 peptide from hTERT (ILAKFLHWL), the RT-pol476 (ILKEPVHGV) peptide from HIV, the HTLV-TAX11 (LLFGYPVYV), and the peptide F271 (FLWGPRALV) derived from
5 MAGE-3 were purchased from Sigma Genosys Biotechnologies (The Woodlands, TX).

Peptide Prediction

10 Binding of peptides to HLA molecules can be predicted for the most common HLA alleles by computational methods (Parker *et al.*, J. Immunol. 152:163-75, 1994; Gulukota *et al.*, J. Mol. Biol. 267:1258-67, 1997). To increase specificity of peptide prediction we used two independent algorithms: a matrix algorithm available on the BIMAS (BioInformatics & Molecular Analysis Section
15 at the NIH) web site (Parker *et al.*, J. Immunol. 152:163-75, 1994) and a linear programming algorithm (LPpep) at Boston University (Z. Weng). BIMAS predicts for the half-life of peptides bound to class I molecules, while LPpep predicts an arbitrary half inhibitory concentration (IC₅₀) in competition with a labeled reference peptide. The output value is listed as ln(IC₅₀).

20

HLA-A*0201 binding assay

TAP-deficient T2 cells were pulsed with 40 µg/ml of peptide and 3 µg/ml of β2-microglobulin (Sigma, St. Louis, MO) for 18 hours in serum-free IMDM (Life Technologies, Rockville, MD) at 37°C. Cells were washed three times in
25 serum-free IMDM and HLA-A*0201 expression was measured by flow cytometry using FITC-conjugated mAb BB7.2 (ATCC). Increase of HLA-A2 expression on T2 cells reflects stabilization of MHC complexes by the addition of exogenous peptides and was quantified using the fluorescence index (FI =
(MFI_{peptide pulsed T2} / MFI_{unpulsed T2}) - 1).

30

Western blot analysis

CYP1B1 expression was determined in microsomal cell fractions. Microsomal protein was isolated by differential speed centrifugation. Cells were harvested, washed, and resuspended in hypotonic buffer. After mechanical
5 homogenization high-density particles were pelleted by centrifugation for 20 minutes at 15,000g. The supernatant was collected and centrifuged for 1 hour at 180,000g. The pellet was resuspended in TEDG buffer, and 100 µg of microsomal protein was separated by SDS-PAGE and transferred to nitrocellulose membrane. Western blot for CYP1B1 was performed according to the
10 manufacturer's recommendations (Gentest, Woburn, MA). Bands were visualized by enhanced chemiluminescent detection (NEN Life Science Products, Boston, MA).

Generation of CTL

15 CTL were generated as previously described (Vonderheide *et al.*, Immunity 10:673-679,1999), CD8⁺ T cells (>80% CD8⁺, >95% CD3⁺, <2.0% CD4⁺, and <5% CD56⁺) were isolated from PBMC by negative selection using magnetic beads. B cells were activated via CD40, and DC were prepared from peripheral blood monocytes with IL-4 and GM-CSF (Schultze *et al.*, J. Clin. Invest.
20 100:2757-2765, 1997). DC were harvested after 7 days, pulsed with peptide (40 µg/ml) and β2-microglobulin (3 µg/ml) for 2 hr at 37°C, irradiated (33 Gy), and added to autologous CD8⁺ T cells at a T:DC ratio of 20:1 in RPMI media supplemented with 10% human AB serum, 2 mM glutamine, 15 µg/ml gentamicin, 20 mM HEPES, and 15 ng/ml IL-7 (Endogen, Woburn, MA). At day
25 7 and weekly thereafter, T cell cultures were harvested and restimulated with irradiated (33 Gy), peptide-pulsed (10 µg/ml) autologous CD40-activated B cells. IL-2 (50 U/ml; Chiron Corp, Emeryville, CA) was introduced on day 8 and replenished as needed every 3–4 days. Flow cytometry was performed as described (Schultze *et al.*, J Clin. Invest. 100:2757-2765, 1997). Assessment of
30 cytotoxic effector function and tetramer analysis were performed with CTL cultures always >90% CD3⁺/CD8⁺, <5% CD4⁺, and <5% CD56⁺.

Cytotoxicity Assay

To assess cytolytic function CTL lines were used after at least four antigenic stimulations in standard ^{51}Cr release assays as previously described (Vonderheide *et al.*, Immunity 10:673-679, 1999). Percent specific lysis was calculated from cpm of (experimental result - spontaneous release)/(maximum release - spontaneous release) x100%. Monocytes as targets were isolated from PBMC by RosetteSep[®] (Stem Cell Technologies, Vancouver) following the manufacturer's recommendations.

Tetramer analysis

Tetrameric A2/peptide complexes with CYP239, CYP246, and TAX11, an immunogenic peptide derived from HTLV-1, were synthesized essentially as described (Altman *et al.*, Science 274: 94-96, 1996) and conjugated to ALEXA-488 (Molecular Probes, Eugene, OR). For staining of CTL lines, cells were incubated with the tetramer and CD8-PE (Beckman Coulter, Fullerton, CA) for 30 minutes at room temperature. Tetramers were also used to sort CYP239-specific CTL. Tetramer sorted CTL were expanded by mitogen stimulation as described (Valmori *et al.*, Cancer Res. 59:2167-2173, 1999).

Use

Use of universal tumor associated antigens in therapeutic methods

As is discussed above, the invention provides methods for preventing or treating conditions associated with excessive cell proliferation and expression of CYP1B1, such as cancer.

Examples of conditions that can be prevented or treated using the methods of the invention, include, for example, all cancers, *e.g.*, melanoma, lymphoma, carcinoma, sarcoma, multiple myeloma, leukemia, lung cancer, ovarian cancer, uterine cancer, cervical cancer, prostate cancer, liver cancer, colon cancer, pancreatic cancer, and brain cancer. Pre-cancerous and non-cancerous conditions characterized by excessive cell proliferation, and expression of a

CYP1B1, can be treated using the methods of the invention as well. For example, all carcinomas *in situ*, e.g., ductal carcinoma *in situ*, lobular carcinoma *in situ*, and cervical carcinoma *in situ*, as well as adenoma and benign polyps can be treated using the methods of the invention.

5 Patients that can be treated using the methods of the invention include those whose conditions are at early, intermediate, or advanced stages of development. Patients can receive treatment according to the invention before, during, or after other types of treatment, such as chemotherapy, radiation, or surgery, or can receive the treatment of the invention in the absence of any other
10 type of treatment. The methods of the invention can also be used as general prophylactic measures; to prevent conditions from arising in patients that are at risk, or have early signs, of developing a condition associated with excessive cellular proliferation, such as cancer; or to prevent recurrence of such a condition. Additional persons that can be treated, in particular, using vaccination methods of
15 the invention (see below), are those who are to donate cells, such as cytotoxic T lymphocytes, for use in the treatment of another (see below).

Central to the prophylactic and therapeutic methods of the invention is the pathway of cell-mediated immunity involving cytotoxic T lymphocytes (CTLs). In this pathway, an antigen is taken up and processed by an antigen
20 presenting cell, so that a peptide of the antigen is presented on the surface of the cell, in the context of MHC. Such antigen presenting cells then activate cytotoxic T lymphocytes, in an MHC-restricted fashion, to proliferate and kill target cells that express the antigen.

The prophylactic and therapeutic methods of the invention intervene in
25 this pathway at different levels. For example, in one of these methods, a CYP1B1 antigen is administered to a patient, in whom the antigen is taken up by antigen presenting cells, which in turn activate CTLs. In another of these methods, an antigen presenting cell is contacted with a CYP1B1 antigen *ex vivo*, where it takes up, processes, and presents the antigen, in the context of MHC. Such *ex vivo*
30 stimulated APCs are then administered to a patient, in whom they specifically activate CTLs. In yet another of these methods, CTLs are activated *ex vivo* with

APCs presenting CYP1B1 peptides, and the activated CTLs are then administered to a patient. These methods, each of which includes numerous variations, are described in further detail below. Also, it is noted that all of these methods can be carried out with CYP1B1 peptides alone or, preferably, in combination with
5 another (or more) tumor associated antigen polypeptides or peptides (*e.g.*, telomerase).

As is noted above, the prophylactic and therapeutic methods of the invention include one in which CYP1B1, or a fragment thereof that binds to MHC, is administered to a patient, in whom the antigen or fragment is taken up
10 by and processed within an antigen presenting cell, which in turn activates a cytotoxic T cell in the patient. This vaccination method can be carried out using CYP1B1, one or more MHC-binding peptides of CYP1B1, and, in addition to these (or a combination thereof), one or more universal TAAs or one or more MHC-binding peptides of more than one universal TAA, or a combination
15 thereof. Optionally, the antigen can be administered in combination with an adjuvant to enhance the anti-TAA immune response, or the antigen can be packaged into a delivery system (see below).

Any reagent including CYP1B1 or a MHC-binding peptide thereof can be used for vaccination. These include, without limitation, full length CYP1B1,
20 MHC-binding fragments of CYP1B1, as well as fusion proteins including CYP1B1 and MHC-binding fragments thereof. Peptides or polypeptides including CYP1B1 peptides and polypeptides can include 8, 9, 10, 11, 12, or more amino acid stretches having sequence identity with a region of CYP1B1. For example, the peptides can include nine amino acid stretches, in which seven,
25 eight, or all nine of the amino acids in the CYP1B1 peptide nine amino acid sequence are identical to a region of nine amino acids in CYP1B1. In addition, a CYP1B1 peptide or polypeptide can include up to 533 amino acids that are identical to an amino acid sequence found in CYP1B1, for example, 9-20, 20-40, 40-80, 80-200, or 200-533 amino acids that are identical to an amino acid
30 sequence found in CYP1B1. Polypeptides containing CYP1B1 peptides can

contain additional amino acid stretches that do not correspond to the amino acid sequence of CYP1B1.

To vaccinate a patient to elicit a CYP1B1-specific immune response in the patient, it is necessary to obtain large amounts of a CYP1B1 protein or peptide, and this can be accomplished by numerous standard methods, for
5 example, chemical synthesis (e.g., Fmoc methods (Sigma Genosys); see above) or expression in eukaryotic or prokaryotic cells.

Recombinant CYP1B1 peptides can be overexpressed *in vivo* by introducing coding sequences of the peptides into various types of cells, or *in*
10 *vitro*, using cell-free expression systems that are known in the art. The peptide products can then be purified for generating CYP1B1-specific CTLs *ex vivo* and for vaccine production. Purified CYP1B1 peptides are also useful for diagnostic assays that measure the presence of CYP1B1-specific CTLs in a test sample. For example, the presence (or increased levels) of CYP1B1-specific CTLs in a sample
15 from a subject who has received an anti-CYP1B1 vaccination, relative to the level of CYP1B1-specific CTLs in a reference sample (such as a pre-vaccination sample from the patient), indicates that the patient has mounted a CYP1B1-specific immune response.

CYP1B1 peptides can be produced by chemical synthesis (e.g., by the
20 methods described in *Solid Phase Peptide Synthesis*, 2nd ed., 1984, The Pierce Chemical Co., Rockford, IL, or by other methods known to those skilled in the art of peptide synthesis).

A wide variety of expression systems can be used to produce recombinant CYP1B1 peptides, polypeptides, fragments, fusion proteins, and amino acid
25 sequence variants. CYP1B1 peptides can be produced in prokaryotic hosts (e.g., *E. coli*) or in eukaryotic hosts (e.g., *S. cerevisiae*, insect cells, such as Sf9 cells, or mammalian cells, such as COS-1, NIH 3T3, or HeLa cells). These cells are commercially available from, for example, the American Type Culture Collection, Rockville, Maryland (also see, e.g., Ausubel *et al.*, *Current Protocols in*
30 *Molecular Biology*, John Wiley & Sons, New York, NY, 1998). The method of transformation and the choice of expression vehicle (e.g., expression vector)

depends on the host system selected. Transformation and transfection methods are described, *e.g.*, by Ausubel *et al.*, *supra*, and expression vehicles can be chosen from the numerous examples that are known in this field.

First, a nucleic acid molecule encoding a CYP1B1 peptide is introduced
5 into a plasmid or other vector, which is then used to transform living cells. Constructs in which a cDNA containing the entire CYP1B1 coding sequence, a fragment of the CYP1B1 coding sequence, amino acid variations of the CYP1B1 coding sequence, or fusion proteins of the aforementioned, inserted in the correct orientation into an expression plasmid, can be used for protein expression.
10 Prokaryotic and eukaryotic expression systems allow various immunogenic domains of CYP1B1 peptides or polypeptides to be recovered as fusion proteins, and then used for the generation of CYP1B1-specific CTLs. In some cases, for example, when a CYP1B1 peptide is to be expressed directly within a patient's cells, it may be desirable to express the CYP1B1 peptide under the control of an
15 inducible or tissue-specific promoter.

Typical expression vectors contain promoters that direct the synthesis of large amounts of mRNA corresponding to the inserted CYP1B1 peptide-encoding nucleic acid molecule in the plasmid-bearing cells. They can also include eukaryotic or prokaryotic "origin of replication" sequences, which allow for their
20 autonomous replication within the host organism, sequences that encode genetic traits that allow vector-containing cells to be selected in the presence of otherwise toxic drugs (such as antibiotics), and sequences that increase the efficiency with which the synthesized mRNA is translated. Stable, long-term vectors can be maintained as freely replicating entities within cells by using regulatory elements
25 of, for example, viruses (*e.g.*, the OriP sequences from the Epstein Barr Virus genome). Cell lines can also be produced that have the vector integrated into genomic DNA, and, in this manner, the gene product is produced on a continuous basis.

Expression of foreign sequences in bacteria such as *Escherichia coli*
30 requires insertion of a nucleic acid molecule encoding a polypeptide into a bacterial expression vector. Plasmid vectors in this category contain several

elements required for propagation of the plasmid in bacteria and expression of inserted DNA of the plasmid by the plasmid-carrying bacteria. Propagation of only plasmid-bearing bacteria is achieved by introducing into the plasmid selectable marker-encoding sequences that allow plasmid-bearing bacteria to grow in the presence of otherwise toxic drugs (*e.g.*, antibiotics). The plasmid also includes a transcriptional promoter that capable of producing large amounts of mRNA from the cloned gene. Such promoters may or may not be inducible promoters. The plasmid also, preferably, contains a polylinker to simplify insertion of the gene in the correct orientation within the vector. For example, in a simple *E. coli* expression vector utilizing the lac promoter, the expression vector plasmid contains a fragment of the *E. coli* chromosome containing the lac promoter and the neighboring *lacZ* gene. In the presence of the lactose analog IPTG, RNA polymerase normally transcribes the *lacZ* gene, producing *lacZ* mRNA, which is translated into the encoded protein, β -galactosidase. The *lacZ* gene can be cut out of the expression vector with restriction endonucleases and replaced by a CYP1B1 peptide gene sequence, or a fragment, fusion, or mutant thereof. When the resulting plasmid is transfected into *E. coli*, addition of IPTG and subsequent transcription from the lac promoter produces mRNA encoding the CYP1B1 polypeptide of interest, which is then translated into a polypeptide.

Once the appropriate expression vector containing a CYP1B1 gene is constructed, it is introduced into an appropriate host cell by transformation, transfection, or transduction techniques that are known in the art, including calcium chloride transformation, calcium phosphate transfection, DEAE-dextran transfection, electroporation, microinjection, protoplast fusion, and liposome-mediated transfection. The host cells that are transformed with the vectors of this invention can include (but are not limited to) *E. coli* or other bacteria, yeast, fungi, insect cells (using, for example, baculoviral vectors for expression), human, mouse, or other animal cells. Mammalian cells can also be used to express CYP1B1 peptides using a vaccinia virus expression system, as is described by Ausubel *et al.*, *supra*.

In vitro expression of CYP1B1 peptides, proteins, fusions, polypeptide fragments, or mutated versions thereof encoded by cloned DNA is also possible using the T7 late promoter expression system. Plasmid vectors containing late promoters and the corresponding RNA polymerases from related bacteriophages such as T3, T5, and SP6 can also be used for *in vitro* production of proteins from cloned DNA. *E. coli* can also be used for expression using an M13 phage such as mGPI-2. Furthermore, vectors that contain phage lambda regulatory sequences, or vectors that direct the expression of fusion proteins, for example, a maltose-binding protein fusion protein or a glutathione-S-transferase fusion protein, also can be used for expression in *E. coli*.

Eukaryotic expression systems permit appropriate post-translational modifications to expressed proteins. Transient transfection of a eukaryotic expression plasmid allows the transient production of CYP1B1 peptides by a transfected host cell. CYP1B1 peptides can also be produced by a stably-transfected mammalian cell line. A number of vectors suitable for stable transfection of mammalian cells are available to the public (*e.g.*, see Pouwels *et al.*, *Cloning Vectors: A Laboratory Manual*, 1985, Supp. 1987), as are methods for constructing such cell lines (see, *e.g.*, Ausubel *et al.*, *supra*). In one example, cDNA encoding a CYP1B1 peptide, protein, fragment, mutant, or fusion protein is cloned into an expression vector that includes the dihydrofolate reductase (DHFR) gene. Integration of the plasmid and, therefore, integration of the CYP1B1 peptide-encoding gene into the host cell chromosome is selected by inclusion of 0.01-300 μ M methotrexate in the cell culture medium (as is described by Ausubel *et al.*, *supra*). This dominant selection can be accomplished in most cell types. Recombinant protein expression can be increased by DHFR-mediated amplification of the transfected gene. Methods for selecting cell lines bearing gene amplifications are described by Ausubel *et al.*, *supra*. These methods generally involve extended culture in medium containing gradually increasing levels of methotrexate. The most commonly used DHFR-containing expression vectors are pCVSEII-DHFR and pAdD26SV(A) (described by Ausubel *et al.*, *supra*). The host cells described above or, preferably, a DHFR-deficient CHO

cell line (*e.g.*, CHO DHFR- cells, ATCC Accession No. CRL 9096) are among those most preferred for DHFR selection of a stably-transfected cell line or DHFR-mediated gene amplification. Other drug markers can be analogously used.

5 Expression of proteins, such as those containing CYP1B1 peptides, in eukaryotic cells allows the production of large amounts of normal or mutant proteins for isolation and purification, and the use of cells expressing a CYP1B1 peptide-containing protein provides a functional assay system for antibodies generated against a CYP1B1 peptide of interest.

10 Another preferred eukaryotic expression system is the baculovirus system using, for example, the vector pBacPAK9, which is available from Clontech (Palo Alto, CA). If desired, this system can be used in conjunction with other protein expression techniques, for example, the myc tag approach described by Evan *et al.* (Mol. Cell Biol. 5:3610-3616, 1985).

15 Once a recombinant CYP1B1 protein is expressed, it can be isolated from the expressing cells by cell lysis followed by protein purification techniques, such as affinity chromatography. In this example, an anti-CYP1B1 peptide antibody, which can be produced by methods that are well-known in the art, can be attached to a column and used to isolate recombinant CYP1B1 peptide-containing proteins.

20 Lysis and fractionation of CYP1B1 peptide-harboring cells prior to affinity chromatography can be performed by standard methods (see, *e.g.*, Ausubel *et al.*, *supra*). Once isolated, the recombinant protein can, if desired, be purified further, *e.g.*, by high performance liquid chromatography (HPLC; *e.g.*, see Fisher, *Laboratory Techniques in Biochemistry and Molecular Biology*, Work and
25 Burdon, Eds., Elsevier, 1980).

 Preferably, CYP1B1 or a MHC-binding peptide thereof is administered to a patient in association with an adjuvant. For example, a chemical antigen (*e.g.*, Freund's incomplete adjuvant; cytoxan; an aluminum compound, such as aluminum hydroxide, aluminum phosphate, or aluminum hydroxyphosphate;
30 liposomes; ISCOMS; microspheres; protein choleates; vesicles consisting of nonionic surfactants; cationic amphiphilic dispersions in water; oil/water

emulsions; muramidyldipeptide (MDP) and its derivatives such as glucosyl muramidyldipeptide (GMDP), threonyl-MDP, murametide and murapalmitin; and QuilA and its subfractions; as well as various other compounds such as monophosphoryl-lipid A (MPLA); gamma-inulin; calcitriol; and loxoribine) can be used.

A biological response modifier, which is a soluble mediator that affects induction of an immune response, can also be used as an adjuvant. For example, cytokines (*e.g.*, IL-2 and GM-CSF), chemokines, co-stimulatory molecules (*e.g.*, B7, ICAM, class I monoclonal antibodies, stem cell factor, and stimulated T cells) can be used. Also, bacterial products, such as toxins or, preferably, subunits or fragments thereof that have reduced (if any) toxicity, but maintained adjuvant activity.

Additional types of adjuvant molecules that can be used in the invention include, for example, biological modifiers of the death response (*e.g.*, apoptosis sensitizers) and compounds or treatment that increases the susceptibility of the target cell to treatment, such as radiation and chemotherapy. Also, increasing expression of CYP1B1 in the cell can increase susceptibility of the cell to treatment according to the invention.

Finally, as is described above, cellular adjuvants can be used in the immunization methods of the invention. For example, a CYP1B1 peptide can be administered to a patient on the surface of an antigen presenting cell, in the context of MHC. In addition to professional antigen presenting cells, *e.g.*, dendritic cells, CD40-activated B cells, irradiated tumor cells (*e.g.*, in association with GM-CSF), alternative antigen presenting cells, synthetic antigen presenting cells (*e.g.*, lipid mycels and artificial APC-like scaffolds), and fusions of any of the above-listed cells can be used.

As an alternative to vaccination with a CYP1B1 protein or peptide, vaccination with a nucleic acid molecule that encodes such a protein or peptide can be used for vaccination. Such nucleic acid molecules can be administered as “naked” DNA molecules, present in a plasmid or viral vector, or packaged into a liposome or cell, such as eukaryotic cell, prior to administration. The nucleic acid

molecules can be administered to a patient *in vivo*, or can be used to treat a cell *ex vivo* (e.g., an antigen presenting cell, such as a dendritic cell or a CD40-activated B cell), which is then administered to the patient. Alternatively, RNA, e.g., mRNA, can be used in these methods (see, e.g., Boczkowski *et al.*, J. Exp. Med. 184:465-472, 1996; J. Exp. Med. 186:1177-1182, 1997).

For *in vivo* expression, a gene that encodes a polypeptide that includes CYP1B1 or an MHC-binding peptide thereof must be delivered to cells in a form that can be taken up by the cells, in which a sufficient level of protein is expressed to induce an effective immune response. Retroviral, adenoviral, lentiviral, poxviral, and other viral vectors are suited as nucleic acid expression vectors for *in vivo* delivery, because they show efficient infection and/or integration and expression; see, e.g., Cayouette *et al.*, Hum. Gene Therapy, 8:423-430, 1997; Kido *et al.*, Curr. Eye Res. 15:833-844, 1996; Bloomer *et al.*, J. Virol. 71:6641-6649, 1997; Naldini *et al.*, Science 272:263-267, 1996; Miyoshi *et al.*, Proc. Nat. Acad. Sci., U.S.A., 94:10319-1032, 1997; *Vaccines: New Approaches to Immunological Problems*, R.W. Ellis (Ed.), Butterworth-Heinemann, Boston. For example, any DNA fragment that encodes a polypeptide that contains a CYP1B1 peptide can be cloned into a retroviral vector and transcribed *via* its endogenous promoter, *via* an exogenous promoter, *via* a promoter specific for the target cell type of interest, or, in the case of retroviral vectors, *via* the retroviral long terminal repeat. Other viral vectors that can be used include adenovirus, adeno-associated virus, poxviruses, such as vaccinia virus or bovine papilloma virus, or a herpes virus, such as Epstein-Barr Virus.

Gene transfer *in vivo* can also be achieved by non-viral means. For example, a plasmid vector that encodes a polypeptide that contains a CYP1B1 peptide can be injected directly into skeletal muscle or cardiac muscle by previously described methods (e.g., Wolff *et al.*, Science, 247:1465-1468, 1990). Expression vectors injected into skeletal muscle *in situ* are taken up into muscle cell nuclei and used as templates for expression of their encoded proteins. CYP1B1 peptide-encoding genes that are engineered to contain a signal peptide are secreted from CYP1B1 peptide-expressing muscle cells, after which they

induce an immune response. Gene transfer into cells within the tissues of a living animal also can be achieved by lipofection (Felgner *et al.*, Proc. Natl. Acad. Sci. USA 84:7413, 1987; Ono *et al.*, Neurosci. Lett. 117:259, 1990; Brigham *et al.*, Am. J. Med. Sci. 298:278, 1989; Staubinger *et al.*, Meth. Enz. 101:512, 1983), or
5 asialoorosomucoid-polylysine conjugation (Wu *et al.*, J. Biol. Chem. 263:14621, 1988; Wu *et al.*, J. Biol. Chem. 264:16985, 1989), and analogous methods.

Retroviral vectors, adenoviral vectors, adenovirus-associated viral vectors, or other viral vectors also can be used to deliver genes encoding CYP1B1 peptides or polypeptides to cells *ex vivo*. Numerous vectors useful for this
10 purpose are generally known (see, *e.g.*, Miller, Human Gene Therapy 15-14, 1990; Friedman, Science 244:1275-1281, 1989; Eglitis *et al.*, BioTechniques 6:608-614, 1988; Tolstoshev *et al.*, Curr. Opin. Biotech. 1:55-61, 1990; Sharp, The Lancet 337:1277-1278, 1991; Cornetta *et al.*, Nucl. Acid Res. and Mol. Biol. 36:311-322, 1987; Anderson, Science 226: 401-409, 1984; Moen, Blood Cells
15 17:407-416, 1991; Miller *et al.*, Biotech. 7:980-990, 1989; Le Gal La Salle *et al.*, Science 259:988-990, 1993; and Johnson, Chest 107:77S-83S, 1995). Retroviral vectors are particularly well developed and have been used in clinical settings (Rosenberg *et al.*, N. Engl. J. Med 323:370, 1990; Anderson *et al.*, U.S. Patent No. 5,399,346).

20 Gene transfer into cells *ex vivo* can also be achieved by delivery of non-viral vectors, such as expression plasmids, using methods such as calcium phosphate or DEAE dextran transfection, electroporation, and protoplast fusion. Liposomes can also be potentially beneficial for delivery of DNA into a cell.

Cells that are to be transduced or transfected *ex vivo* can be obtained from
25 a patient (*e.g.*, peripheral blood cells, such as B cells or dendritic cells, bone marrow stem cells, or cells from a tumor biopsy) prior to transfection, and re-introduced after transfection. However, the cells also can be derived from a source other than the patient undergoing gene transfer.

In the constructs described above, CYP1B1 peptide expression can be
30 directed from any suitable promoter (*e.g.*, the human cytomegalovirus (CMV), simian virus 40 (SV40), or metallothionein promoters), and regulated by any

appropriate mammalian regulatory element. For example, if desired, enhancers known to preferentially direct gene expression in skeletal muscle cells can be used to direct CYP1B1 peptide expression for vaccination *in situ*. The enhancers used can include, without limitation, those that are characterized as tissue- or cell-specific in their expression.

Conventional pharmaceutical practice can be employed to provide suitable formulations or compositions to administer CYP1B1 peptide or nucleic acid vaccinations for treatment of, or prophylaxis against, cancer. CYP1B1 peptides, CYP1B1 polypeptides, and CYP1B1 nucleic acid molecules can be administered within a pharmaceutically-acceptable diluent, carrier, or excipient, in unit dosage form. Administration can begin before a patient is symptomatic. Any appropriate route of administration can be employed, for example, administration can be parenteral, intravenous, intra-arterial, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, by suppositories, or oral administration. Therapeutic formulations can be in the form of liquid solutions or suspensions; for oral administration, formulations can be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols. An adjuvant, *e.g.*, as listed above, can be included with the formulation.

Methods well known in the art for making formulations are found, for example, in *Remington's Pharmaceutical Sciences*, (18th edition), ed. A. Gennaro, 1990, Mack Publishing Company, Easton, PA. Formulations for parenteral administration can, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers can be used to control the release of the compounds. Other potentially useful parenteral delivery systems for CYP1B1 peptides, polypeptides, and CYP1B1 nucleic acid molecules include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation can contain excipients, for example, lactose, or can be aqueous

solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or can be oily solutions for administration in the form of nasal drops, or as a gel.

As is mentioned above, in addition to the vaccination methods described above, which result in the activation of antigen-specific, MHC-restricted CTLs *in vivo*, such cells (*i.e.*, antigen-specific, MHC-restricted CTLs) can be generated *in vitro*, and then administered to patients. Any cell that expresses an endogenous or exogenously-introduced major histocompatibility antigen-encoding gene can be used to present a CYP1B1 peptide to generate CYP1B1-specific CTLs *in vitro*.
In one variation of this approach, a peptide-presenting cell expresses an endogenously or exogenously-introduced CYP1B1 polypeptide-encoding gene. Expression of endogenous CYP1B1 in antigen-presenting cells can be stimulated as described in Schultze *et al.*, *supra*, by cytokines, such as IL-2, or by other molecules that are known to those of skill in this art to stimulate CYP1B1 expression.

In another variation, the antigen presenting cells are pulsed with CYP1B1 or MHC-binding peptide thereof, and the pulsed cells are then used to generate CTLs for administration to a patient. Preferably, the CTLs used in these methods are obtained from the patient to whom they are to ultimately be administered (*i.e.*, the cells are autologous). Alternatively, donor cells (*i.e.*, allogeneic cells) can be used in this method.

Finally, methods in which any of the above-described immunotherapeutic approaches are combined are included in the invention. For example, a patient may be treated with an *ex vivo*, CYP1B1-activated CTL and/or an *ex vivo*, CYP1B1-pulsed APC (*e.g.*, a DC or a CD40-activated B cell), and this treatment can be carried out before, during, or after a vaccination approach (see above). In addition to combining the approaches, each approach (or a combination thereof) can employ multiple peptides of CYP1B1, peptides of other TAAs, or a combination thereof.

30

Measurement of CYP1B1-specific CTL levels in patients, CTL donors, and CYP1B1-specific CTL preparations generated ex vivo

Patients who have one or more tumors containing CYP1B1-expressing tumor cells and patients who are at risk for developing such tumors can be vaccinated with compositions containing one or more CYP1B1 peptides, CYP1B1 polypeptides, CYP1B1 nucleic acid molecules, cells presenting a CYP1B1 peptide, or mixtures thereof (other TAA (*e.g.*, hTERT) polypeptides, peptides, nucleic acid molecules, or APCs can also be included). Subjects to be used as donors of CYP1B1-specific CTLs for transfer into patients can be similarly vaccinated. Levels of CYP1B1-specific CTLs that result from CYP1B1-specific vaccination of patients or other subjects, or *ex vivo* generation of CYP1B1 specific CTLs, can be monitored using well-known methods. An increase in the level of CYP1B1-specific CTLs in a test sample from a vaccinated subject or a CTL culture stimulated with CYP1B1 *ex vivo*, relative to a reference sample (*e.g.*, a pre-vaccination or pre-stimulation sample), indicates that a CYP1B1-specific CTL response has been stimulated in a vaccinated subject or CYP1B1-stimulated CTL culture. Preferably the increase is by at least 50%, more preferably, at least 100%, still more preferably, at least 200%, and most preferably, at least 400%. In addition, the efficacy of non-antigen-specific immunotherapies (*e.g.*, administration of IL-2 or interferon) against tumors containing CYP1B1-expressing cells can be monitored using similar approaches.

Levels of CYP1B1-specific CTLs can also be assessed in naive subjects who have not received CYP1B1 vaccinations or other treatment for the purpose of generating CYP1B1-specific CTLs. Since some types of tumors (*e.g.*, malignant melanoma, renal cell carcinoma, and non-Hodgkin's lymphoma) themselves elicit immune responses in their hosts, an increase in the level of CYP1B1-specific CTLs cells in a patient sample, compared to the level in a reference sample from a normal subject who does not have a tumor, or in a reference sample that was previously obtained from the patient, can indicate the development of a tumor in a patient not known to have a tumor or an increase in tumor burden (*e.g.*, increased

tumor size, or the development or increase in metastatic tumors) in a patient known to have a tumor.

One approach by which the level of CYP1B1-specific CTLs can be measured is using standard cytotoxicity assays, such as the Cr⁵¹ release assay (Schultze *et al.*, J. Clin. Invest. 100:2757, 1997), which is described above.

Another approach for measuring the level of CYP1B1-specific CTLs involves measuring the binding of peptide-specific CTLs to a tetrameric peptide/MHC complex *in vitro*, as is described by Altman *et al.* (Science 274:94-96, 1996).

Briefly, a fusion protein containing an HLA heavy chain molecule, such as

HLA-A*0201, plus a peptide that is a substrate for biotinylation at the C-terminus of the HLA polypeptide, is produced. The fusion protein is folded *in vitro* in the presence 2-microglobulin and a CYP1B1 peptide ligand. The purified MHC/CYP1B1 peptide complexes are then biotinylated at the C-terminus of the HLA heavy chain, and tetramers are produced by mixing the biotinylated

MHC/CYP1B1 peptide complexes with phycoerythrin-labeled deglycosylated avidin at a molar ratio of 4:1. Samples that contain CTLs (such as blood samples or *ex vivo* cultures) are mixed with the CYP1B1 peptide/MHC tetrameric complexes and the relative amount of CYP1B1-specific CTLs that bind to the CYP1B1 peptide/MHC tetrameric complexes can be measured for each sample by flow cytometry, using methods described by Altman *et al.*, *supra*, and by other methods known to those of skill in this art. Another method that can be used is ELISPOT (Herr *et al.*, J. Immunol. Methods 203:141-152, 1997).

Other Embodiments

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication or patent application was specifically and individually indicated to be incorporated by reference.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications, and this application is intended to cover any variations, uses, or

adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure come within known or customary practice within the art to which the invention pertains and can be applied to the essential features hereinbefore set forth, and follows in the scope of

5 the appended claims.

What is claimed is:

APPENDIX A

Search Report

HLA-A*0201 Nonamers

HLA-A*0201 Decamers

HLA-A*0201 Octamers

HLA-A*0202 Nonamers

HLA-A*0202 Decamers

HLA-A*0203 Nonamers

HLA-A*0203 Decamers

HLA-A*0203 Octamers

HLA-A1 Nonamers

HLA-A1 Decamers

HLA-A26 Nonamers

HLA-A26 Decamers

HLA-B*0702 Nonamers

HLA-B*0702 Decamers

HLA-B*1510 Nonamers

HLA-B*2705 Nonamers

HLA-B8 Octamers

HLA-B8 Nonamers

HLA-A*0201 Nonamers

HLA-A1 Nonamers

HLA-B*0702 Nonamers

HLA-B*2705 Nonamers

Pos 1 2 3 4 5 6 7 8 9

25 LLLSVLATV

22 TLLLLLSVL

528 LLDSAVQNL

479 QLFLFISIL

190 FLDPRPLTV

377 NLPYVLAFL

344 LLFTRYPDV

334 TLSTALQWL

239 SLVDVMPWL

58 PLIGNAAAV

24 LLLSVLAT

21 TLLLLLSV

170 VLSEARELV

17 SIQQTLLL

521 TLRESMELL

510 TIKPKSFKV

196 LTVVAVANV

76 RLARRYGDV

Pos 1 2 3 4 5 6 7 8 9

372 MGDQPNLPY

241 VDVMPWLQY

404 TANTSVLGY

190 FLDPRPLTV

185 SADGAFLDP

174 ARELVALLV

171 LSEARELVA

165 VLEGHVLSE

7 PNDPWPLNP

445 FLDKDG LIN

341 WLLLLFTRY

522 LRESMELL

336 STALQWLLL

218 DPEFRELLS

206 SAVCFGCRY

129 GRSMAGHY

439 NFDPARFLD

378 LPYVLAFLY

Pos 1 2 3 4 5 6 7 8 9

192 DPRPLTVVA

51 PPGPFAWPL

414 IPKDTVVFV

375 QPNLPYVLA

288 APRDMMDAF

399 IPHATTANT

250 FPNPVRTVF

194 RPLTVVAVA

512 KP KSF KVN V

50 APPGPFAWP

320 VPATITDIF

117 RPAFASFRV

89 LGSCPIVVL

57 WPLIGNAAA

474 ELSKMQLFL

395 VPVTIPHAT

183 RGSADGAFL

309 HGGGARLDL

Pos 1 2 3 4 5 6 7 8 9

232 GRTVGAGSL

37 QRLLRQRRR

443 ARFLDKDGL

258 FREFEQLNR

145 RRAAHSM MR

79 RRYGDVFQI

347 TRYPDVQTR

467 KRRCIGEEL

265 NRNFSNFIL

116 DRPAFASFR

514 KSFKVNVTL

469 RCIGEELSK

182 VRGSADGAF

129 GRSMAGHY

47 LRSAPPGPF

40 LRQRRRQLR

175 RELVALLVR

144 QRRAAHSM

39 LLRQRRRQL
525 SMELLD SAV
337 TALQWLLLL
246 WLQYFPNPV
235 VGAGSLVDV
172 SEARELVAL
23 LLLLLSVLA
470 CIGEELSKM
380 YVLAFLYEA
316 DLENVPATI
292 MMDAFILSA
173 EARELVALL
88 RLGSCPIVV
64 AAVGQAAHL
520 VTLRESMEL
336 STALQWLLL
312 GARLDLENV
249 YFPNPVRTV
200 AVANVMSAV
165 VLEGHVLS
89 LGSCPIVVL
15 PLSIQQTTL
481 FLFISILAH
474 ELSKMQLFL
419 VVFNQWSV
414 IPKDTVVFV
381 VLAFLYEA
373 GDQPNLPYV
355 RVQAELDQV
338 ALQWLLLLF
282 SLRPGAAPR
169 HVLSEAREL
95 VVLNGERAI
86 QIRLGSCPI
69 AAHLSFARL
451 LINKDLTSR
450 GLINKDLTS
412 YHIPKDTV
409 VLGYPHIPK
402 ATTANTSVL
342 LLLLFTYR
322 ATITDIFGA
272 ILDKFLRHC
191 LDPRPLTV
87 IRLGSCPIV
55 FAWPLIGNA
18 IQQTTLTLL
514 KSFKVNVTL
501 AKMNFSYGL
460 VMIFSVGKR
457 TSRVMIFSV
356 VQAELDQVV
319 NVPATITDI
315 LDLENVPAT
314 RLDLENVPA
297 ILSAEKKA
296 FILSAEKKA
233 RTVGAGSLV
188 GAFLDPRPL

324 ITDIFGASQ
258 FREFEQLNR
216 HDDPEFREL
73 SFARLARRY
499 EPAKMNFYSY
292 MMDAFILSA
137 YSEHWKVQR
81 YGDVFQIRL
349 YPDVQTRVQ
497 PNEPAKMNF
428 NHDPLKWP
415 PKDTVVFVN
359 ELDQVVGRD
228 NEEFGRTVG
20 QTTLTLLLS
530 DSAVQNLQA
447 DKDGLINKD
316 DLENVPATI
215 SHDDPEFRE
33 VHVGRQLLR
528 LLDSAVQNL
525 SMELLD SAV
505 FSYGLTIKP
456 LTRVMIFS
393 SFVPVTIPH
376 PNLPYVLA
333 DTLSTALQW
331 SQDTLSTAL
314 RLDLENVPA
305 AGDSHGGGA
299 SAEKKAAGD
240 LVDVMPWLQ
114 FADRPFAFAS
21 TTLLTLLSV
476 SKMQLFLFI
471 IGEELSKMQ
453 NKDLTSRVM
397 VTIPHATTA
385 LYEAMRFSS
365 GRDRLP
357 QAELDQVVG
279 HCESLRPGA
272 ILDKFLRHC
260 EFEQLNRNF
227 HNEEFGRTV
221 FRELLSHNE
91 SCPIVVNLG
90 GSCPIVVNL
490 QCDFRANPN
472 GEELSKMQL
440 FPARFLDK
436 NPENFDPAR
426 SVNHDPLKW
353 QTRVQAELD
338 ALQWLLLLF
289 PRDMMDAFI
271 FILDKFLRH
233 RTVGAGSLV
98 NGERAIHQA

14 NPLSIQQT
438 ENFDPARFL
402 ATTANTSVL
173 EARELVALL
64 AAVGQAAHL
48 RSAPPGPFA
514 KSFKVNVTL
467 KRRCIGEEL
370 PCMGDQPNL
307 DSHGGGARL
172 SEARELVAL
159 QPRSRQVLE
99 GERAIHQAL
69 AAHLSFARL
8 NDPWPLNPL
6 SPNDPWPLN
501 AKMNFSYGL
499 EPAKMNFYSY
496 NPNEPAKMN
424 QWSVNHDPL
349 YPDVQTRVQ
346 FTRYPDVQT
336 STALQWLLL
331 SQDTLSTAL
327 IFGASQDTL
284 RPGAAPRDM
216 HDDPEFREL
189 AFLDPRPLT
163 RQVLEGHVL
158 RQPRSRQVL
115 ADPFAFASF
53 GPFAPWPLIG
47 LRSAPPGPF
39 LLRQRRRQL
31 ATVHVGRQL
18 IQQTTLTLL
17 SIQQTTLTLL
15 PLSIQQTTL
11 WPLNPLSIQ
528 LLDSAVQNL
521 TLRESMELL
448 KDGLINKDL
443 ARFLDKDGL
436 NPENFDPAR
430 DPLKWPNP
390 RFSSFPVPT
377 NLPYVLAFL
337 TALQWLLLL
334 TLSTALQWL
290 RDMMDAFIL
229 EEFGRTVGA
218 DPEFRELLS
148 AHSMRNFF
19 QQTTLTLL
16 LSIQQTTL
9 DPWPLNPLS
493 FRANPNEPA
476 SKMQLFLFI
441 DPARFLDKD

479 QLFLFISIL
472 GEELSKMQL
383 AFLYEAMRF
295 AFILSAEKK
289 PRDMMDAFI
163 RQVLEGHVL
43 RRRQLRSAP
509 LTIKPKSFK
370 PCMGDQPNL
307 DSHGGGARL
294 DAFILSAEK
213 RYSHDDPEF
188 GAFLDPRPL
153 RNFFTRQPR
87 IRLGSCPIV
72 LSFARLARR
44 RRQLRSAPP
36 GQRLLRQRR
22 TLLTLLSVL
520 VTLRESMEL
494 RANPNEPAK
481 FLFISILAH
468 RRCIGEELS
461 MIFSVGKRR
460 VMIFSVGKR
459 RVMIFSVGK
451 LINKDLTSR
446 LDKDGLINK
341 WLLLLFTYR
340 QWLLLLFT
337 TALQWLLLL
313 ARDLENVNP
283 LPGAAPRD
260 EFEQLNRNF
247 LQYFPNPVR
161 RSRQVLEGH
158 RQPRSRQVL
124 RVVSGGRSM
89 LGSCPIVVL
69 AAHLSFARL
64 AAVGQAAHL
16 LSIQQTTL
508 GLTIKPKSF
504 NFSYGLTIK
497 PNEPAKMNF
474 ELSKMQLFL
448 KDGLINKDL
438 ENFDPARFL
408 SVLGYPHIPK
389 MRFSSFPV
382 LAFLYEA
376 PNLPYVLA
361 DQVVGRDRL
358 AELDQVVGR
352 VQTRVQAEL
327 IFGASQDTL
306 GDHGGGAR
290 RDMMDAFIL
282 SLRPGAAPR

180 LLVRGSADG	48 RSAPPGPFA	434 WPNPENFDP	277 LRHCESLRP
131 SMAFGHYSE	31 ATVHVQGRL	413 HIPKDTVVF	275 KFLRHCESL
102 AIHQALVQQ	17 SIQQTLL	376 PNLPYVLA	269 SNFILDKFL
96 VLNGERAIH	516 FKVNVTLRE	374 DQPNLPYVL	256 TVFREFEQL
32 TVHVQGRL	379 PYVLAFLYE	369 LPCMGDQPN	250 FPNPVRTVF
31 ATVHVQGRL	291 DMDAFILS	361 DQVVGRDRL	221 FRELLSHNE
29 VLATVHVGO	282 SLRPGAAPR	352 VQTRVQAE	219 PEFRELLSH
27 LSVLATVHV	266 RNFSNFILD	335 LSTALQWLL	208 VCFGCRYSH
16 LSIQQTLL	250 FPNPVRTVF	329 GASQDTLST	202 ANVMSAVCF
8 NDPWPLNPL	234 TVGAGSLVD	314 RLDLENVPA	183 RGSADGAFL
452 INKDLTSRV	160 PRSRQVLEG	297 ILSAEKKA	174 ARELVALLV
401 HATTANTSV	156 FTRQPRSRQ	275 KFLRHCESL	169 HVLSEAREL
397 VTIPHATTA	101 RAIHQALVQ	269 SNFILDKFL	132 MAFGHYSEH
307 DSHGGGARL	12 PLNPLSIQQ	256 TVFREFEQL	106 ALVQQGSAF
275 KFLRHCESL	503 MNFSYGLTI	252 NPVRTVFRE	81 YGDVVFQIRL
256 TVFREFEQL	481 FLFISILAH	244 MPWLQYFPN	80 RYGDVVFQIR
199 VAVANVMSA	475 LSKMQLFLF	239 SLVDVMPWL	78 ARRYGDVFO
179 ALLVRGSAD	408 SVLGYHIPK	235 VGAGSLVDV	31 ATVHVQGRL
79 RRYGDVFI	403 TTANTSVLG	217 DDPEFRELL	15 PLSIQQTLL
19 QQTLLLLL	402 ATTANTSVL	191 LDPRPLTVV	531 SAVQNLQAK
4 SLSPNDPWP	392 SSFVPVTIP	188 GAFLDPRPL	506 SYGLTIKPK
486 ILAHQCDFR	363 VVGRDRLP	125 VVSGGRSMA	485 SILAHQCDF
477 KMQLFLFIS	346 FTRYPDVQT	113 AFADRPAFA	470 CIGEELSKM
443 ARFLDKDGL	337 TALQWLLLL	81 YGDVVFQIRL	458 SRVMIFSVG
411 GYHIPKDTV	318 ENVPATITD	22 TLLLLLSVL	444 RFLDKDGLI
406 NTSVLGYHI	309 HGGGARLDL	5 LSPNDPWPL	421 FVNQWSVNH
394 FVPVTIPHA	307 DSHGGGARL	520 VTLRESMEL	413 HIPKDTVVF
384 FLYEAMRFS	184 GSADGAFLD	513 PKSFKVNV	365 GRDRLP
352 VQTRVQAE	121 ASFRVVSGG	479 QLFLFISIL	354 TRVQAE
343 LLLFTRYPD	115 ADRPAFASF	472 GEELSKMQL	338 ALQWLLLLF
331 SQDTLSTAL	71 HLSFARLAR	454 KDLTSRVM	335 LSTALQWLL
329 GASQDTLST	49 SAPPGPFAW	396 PVTIPHATT	331 SQDTLSTAL
327 IFGASQDTL	24 LLLLSVLAT	391 FSSFVPVTI	271 FILDKFLRH
326 DIFGASQDT	19 QQTLLLLL	389 MRFSSFPV	270 NFILDKFLR
271 FILDKFLRH	18 IQQTLLLL	378 LPYVLAFLY	268 NFSNFDKF
236 GAGSLVDVM	16 LSIQQTLL	338 ALQWLLLLF	267 NFSNFILDK
232 GRTVGAGSL	520 VTLRESMEL	317 LENVPATIT	236 GAGSLVDVM
227 HNEEFGRTV	514 KSFKVNVTL	305 AGDSHGGGA	223 ELLSHNEEF
216 HDDPEFREL	509 LTIKPKSKF	292 MMDAFILSA	173 EARELVALL
193 PRPLTVVAV	478 MQLFLFISI	265 NRNFNFIL	138 SEHWKVQRR
177 LVALLVRGS	474 ELSKMQLFL	249 YFPNPVRTV	126 VSGGRSMAF
176 ELVALLVRG	469 RCIGEELSK	233 RTVGAGSLV	123 FRVVS
135 GHYSEHWKV	463 FSVGKRRCI	232 GRTVGAGSL	115 ADRPAFASF
107 LVQQGSFA	450 GLINKDLTS	213 RYSHDDPEF	112 SAFADRPAF
512 KPKSFKVNV	417 DTVVFVNQW	202 ANVMSAVCF	99 GERAIHQAL
503 MNFSYGLTI	412 YHIPKDTV	200 AVANVMSAV	93 PIVVLNGER
502 KMNFSYGLT	406 NTSVLGYHI	193 PRPLTVVAV	75 ARLARRYGD
476 SKMQLFLFI	391 FSSFVPVTI	190 FLDPRLTV	63 AA
467 KRRCIGEEL	322 ATITDIFGA	181 LVRGSADGA	33 VHVQGRLLR
454 KDLTSRVM	308 SHGGGARLD	174 ARELVALLV	32 TVHVQGRL
389 MRFSSFPV	268 FSNFILDKF	171 LSEARELVA	528 LLDSAVQNL
387 EAMRFSFV	205 MSAVCFGCR	169 HVLSEAREL	515 SFKVNVTLR
341 WLLLLFTRY	196 LTVVAVANV	126 VSGGRSMAF	501 AKMNFSYGL
339 LQWLLLLFT	175 RELVALLVR	112 SAFADRPAF	495 ANPNEPAKM
330 ASQDTLSTA	83 DVFQIRLGS	106 ALVQQGSAF	473 EELSKMQLF
309 HGGGARLDL	66 VGQAALHSF	92 CPIVVLNGE	437 PENFDPARF
269 SNFILDKFL	9 DPWPLNPLS	87 IRLGSCPIV	432 LKWPNPENF
181 LVRGSADGA	4 SLSPNDPWP	79 RRYGDVFI	425 WSVNHDPLK
178 VALLVRGSA	523 RESMELDS	77 LARRYGDVF	402 ATTANTSVL

162 SRQVLEGHV	510 TIKPKSFKV	62 NAAAVGQAA	377 NLPYVLAFL
150 SMMRNFFTR	480 LFLFISILA	58 PLIGNAAAV	374 DQPNLPYVL
125 VVSGGRSMA	458 SRVMIFSVG	56 AWPLIGNAA	372 MGDQPNLPY
106 ALVQQGSAF	446 LDKDGLINK	32 TVHVGQRLL	367 DRLPCM GDQ
81 YGDVVFQIRL	425 WSVNHDPLK	24 LLLSVLAT	309 HGGGARLDL
63 AAAVGQAAH	407 TSVLGYHIP	530 DSAVQNLQA	263 QLNRFNFSNF
28 SVLATVHV	354 TRVQAELDQ	503 MNFSYGLTI	239 SLVDVMPWL
26 LLSVLATVH	339 LQWLLLLFT	463 FSVGKRRCI	216 HDDPEFREL
527 ELLDSAVQN	335 LSTALQWLL	412 YHIPKDTV	212 CRYSHDDPE
517 KVNVTLRES	329 GASQDTLST	411 GYHIPKDTV	197 TVVAVANVM
508 GLTIKPKSF	311 GGARLDLEN	406 NTSVLGYHI	193 PRPLTVVAV
485 SILAHQCDF	281 ESLRPGAAP	387 EAMRFSSFV	172 SEARELVAL
478 MQLFLFISI	277 LRHCESLRP	350 PDVQTRVQA	160 PRSRQVLEG
463 FSVGKRRCI	267 NFSNFILDK	339 LQWLLLLFT	157 TRQPRSRQV
455 DLTSRVMIF	255 RTVFREFEQ	315 LDLENVPAT	147 AAHSMMRNF
445 FLDKDGLIN	219 PEFRELLSH	289 PRDMMDAFI	137 YSEHWKVQR
444 RFLDKDGLI	214 YSHDDPEFR	280 CESLRPGAA	100 ERAIHQALV
413 HIPKDTVVF	161 RSRQVLEGH	264 LNRNFSNFI	51 PPGPFAWPL
391 FSSFVPVTI	126 VSGGRSMAF	253 PVRTVFREF	39 LLRQRRRQL
358 AELDQVVGR	125 VVSGGRSMA	248 QYFPNPVRT	35 VQQRLLRQR
335 LSTALQWLL	88 RLGSCPIVV	170 VLSEARELV	26 LLSVLATVH
264 LNRNFSNFI	53 GPFAPWPLIG	118 PAFASFRVV	19 QQTTLTLLL
224 LLSHNEEFG	50 APPGPFAPW	100 ERAIHQALV	18 IQQTTLTLLL
217 DDPEFRELL	41 RQRRRQLRS	88 RLGSCPIVV	17 SIQQTTLTLLL
194 RPLTVVAVA	34 HVGQRLLRQ	86 QIRLGSCPI	8 NDPWPLNPL
183 RGSADGAFL	10 PWPLNPLSI	67 GQAAHLSFA	521 TLRESMELL
174 ARELVALLV	3 TSLSPNDPW	66 VGQAAHLSF	499 EPAKMNFYSY
166 LEGHVLSEA	2 GTSLSPNDP	61 GNAAAVGQA	493 FRANPNEPA
164 QVLEGHVLS	515 SFKVNVTLR	27 LSVLATVHV	455 DLTSRVMIF
157 TRQPRSRQV	465 VGKRRRCIGE	524 ESMELLD SA	454 KDLTSRVM I
124 RVVSGGRSM	434 WPNPENFDP	457 TSRVMIFSV	436 NPENFDPA R
120 FASFRVVS	416 KDTVVFVNQ	452 INKDLTSRV	393 SFVPVTIPH
118 PAFASFRVV	386 YEAMRFSSF	435 PNPENFDPA	386 YEAMRFSSF
105 QALVQQGSA	347 TRYPDVQTR	397 VTIPHATTA	378 LPYVLAFLY
99 GERAHQAL	330 ASQDTLSTA	386 YEAMRFSSF	336 STALQWLLL
59 LIGNAAAVG	328 FGASQDTLS	383 AFLYEAMRF	284 RPGAAPRDM
46 QLRSA PGP	286 GAAPRDMMD	373 GDQPNLPYV	259 REFEQLNRN
38 RLLRQRRRQ	253 PVRTVFREF	356 VQAELDQVV	253 PVRTVFREF
5 LSPNDPWPL	239 SLVDVMPWL	355 RVQAELDQV	242 DVMPWLQYF
535 NLQAKETCQ	238 GSLVDVMPW	348 RYPDVQTRV	241 VDVPWLQY
532 AVQNLQAKE	226 SHNEEFGR	330 ASQDTLSTA	186 ADGAFDPR
531 SAVQNLQAK	192 DPRPLTVVA	326 DIFGASQDT	167 EGHVLSEAR
524 ESMELLD SA	189 AFLDPRPLT	322 ATITDIFGA	148 AHSMMRNFF
483 FISILAHQC	170 VLSEARELV	319 NVPATITDI	141 WKVQRRRAH
408 SVLGYHIPK	150 SMMRNFFTR	312 GARLDLENV	128 GGRSMAFGH
404 TANTSVLGY	149 HSMMRNFFT	287 AAPRDMMDA	122 SFRVVSGGR
398 TIPHATTAN	130 RSMAFGHYS	279 HCESLRPGA	96 VLNGERAIH
374 DQPNLPYVL	106 ALVQQGSAF	242 DVMPWLQYF	73 SFARLARRY
370 PCMGDQPNL	80 RYGDVVFQIR	199 VAVANVMSA	68 QAAHLSFAR
364 VGRDRLPCM	55 FAWPLIGNA	196 LTVVAVANV	66 VGQAAHLSF
361 DQVVGRDRL	54 PFAWPLIGN	182 VRGSADGAF	42 QRRRQLRSA
359 ELDQVVGRD	6 SPNDPWPLN	149 HSMMRNFFT	30 LATVHVQQR
348 RYPDVQTRV	529 LDSAVQNLQ	147 AAHSMMRNF	522 LRESMELL
346 FTRYPDVQT	524 ESMELLD SA	140 HWKVQRRRA	518 VNVTLRESM
324 ITDIFGASQ	511 IKPKSFKVN	139 EHVKVQRRRA	503 MNFSYGLTI
303 KAAGDSHGG	507 YGLTIKPKS	111 GSAFADRPA	486 ILAHQCDFR
290 RDMMDAFIL	494 RANPNEPAK	107 LVQQGSAFA	478 MQLFLFISI
276 FLRHCESLR	488 AHQCDFRAN	94 IVVLNGERA	475 LSKMQLFLF
263 QLNRFNFSNF	484 ISILAHQCD	76 RLARRYGDV	453 NKDLTSRVM

243 VMPWLQYFP	468 RRCIGEELS	70 AHLSEFARLA	440 FDPARFLDK
223 ELLSHNEEF	460 VMIFSVGKR	42 QRRRQLRSA	405 ANTSLVGYH
189 AFLDPRPLT	457 TSRVMIFSV	23 LLLLLSVLA	404 TANTSVLGY
163 RQVLEGHVL	432 LKWPNPENF	21 TTLLLLLSV	360 LDQVVGRDR
117 RPAFASFRV	420 VVFVNQWSVN	10 PWPLNPLSI	348 RYPDVQTRV
113 AFADRPFA	409 VLGYHIPKD	525 SMELLD SAV	334 TLSTALQWL
100 ERAIHQALV	373 GDQPNLPYV	510 TIKPKSFKV	320 VPATITDIF
71 HLSFARLAR	371 CMGDQPNLP	502 KMNFSYGLT	319 NVPATITDI
67 GQAAHLSFA	367 DRLPCM GDQ	497 PNEPAKMNF	288 APRDMM DAF
62 NAAAVGQAA	358 AELDQVVGR	485 SILAHQCDF	276 FLRHCESLR
61 GNAAAVGQA	321 PATITDIFG	478 MQLFLFISI	251 PNPVRTVFR
57 WPLIGNAAA	298 LSAEKKAAG	473 EELSKMQLF	225 LSHNEEFGR
49 SAPP GPFAW	276 FLRHCESLR	455 DLTSRVMIF	217 DDPEFRELL
12 PLNPLSIQQ	263 QLNRNFSNF	444 RFLDKDGLI	206 SAVCFGCYR
495 ANPNEPAKM	249 YFPNPVRTV	437 PENFDPARF	162 SRQVLEGHV
487 LAHQCD FRA	248 QYFPNPVRT	432 LKWPNPENF	155 FFTRQPRSR
482 LFISILAHQ	245 PWLQYFPNP	401 HATTANTSV	152 MRNFFTRQP
472 GEELSKMQL	242 DVMPWLQYF	394 FVPVTIPHA	150 SMMRNFFTR
448 KDGLINKDL	237 AGSLVDVMP	380 YVLAFLYEA	134 FGHYSEHWK
438 ENFDPARFL	231 FGRTVGAGS	372 MGDQPNLPY	109 QQGSADFAD
431 PLKWPNPEN	225 LSHNEEFGR	344 LLFTRYPDV	77 LARRYGDVF
426 SVNHDPLKW	194 RPLTVVAVA	316 DLENVPATI	71 HLSFARLAR
424 QWSVNHDPL	178 VALLVRGSA	281 ESLRPGAAP	5 LSPNDPWPL
399 IPHATTANT	164 QVLEGHVLS	263 QLNRNFSNF	476 SKMQLFLFI
390 RFSSFPVPT	157 TRQPRSRQV	260 EFEQLNRNF	463 FSVGKRRCI
382 LAFLYEAMR	131 SMAFGHYSE	246 WLQYFPNPV	424 QWSVNHDPL
371 CMGDQPNLP	122 SFRVVS GGR	227 HNEEFGRTV	364 VGRDRLPCM
368 RLPCM GDQP	118 PAFASFRVV	226 SHNEEFGRT	254 VRTVREFE
298 LSAEKKAAG	111 GSAFAD RPA	223 ELLSHNEEF	222 RELLSHNEE
287 AAPRDMMDA	97 LNGERAIHQ	178 VALLVRGSA	214 YSHDDPEFR
265 NRNFSNFIL	96 VLNGERAIH	166 LEQHVLS EA	205 MSAVCFGCR
242 DVMPWLQYF	82 GDVFQIRLG	157 TRQPRSRQV	194 RPLTVVAVA
204 VMSAVCFGC	72 LSFARLARR	119 AFASFRVVS	143 VQRRAAHSM
192 DPRPLTVVA	69 AAHLSFARL	95 VVLNGERAI	95 VVLNGERAI
158 RQPRSRQVL	64 AAVGQAAHL	78 ARRYGDVFQ	86 QIRLGSCPI
94 IVVLNGERA	51 PGPFAWPL	55 FAWPLIGNA	450 GLINKDLTS
51 PGPFAWPL	38 RLLRQRRRQ	52 PGPFAWPLI	447 DKDGLINKD
48 RSAPP GPFA	32 TVHVGQRLL	25 LLLSVLATV	391 FSSFPVPTI
42 QRRRQLRSA	29 VLATVHVQG	533 VQNLQAKET	381 VLAFLYEAM
13 LNPLSIQQT	28 SVLATVHVG	508 GLTIKPKSF	316 DLENVPATI
509 LTIKPKSFK	27 LSVLATVHV	487 LAHQCD FRA	301 EKKAAGDSH
505 FSYGLTIKP	5 LSPNDPWPL	480 LFLFISILA	285 PGAAPRDMM
494 RANPNEPAK	533 VQNLQAKET	475 LSKMQLFLF	168 GHVLSEARE
459 RVMIFSVGK	532 AVQNLQAKE	449 DGLINKDLT	135 GHYSEHWKV
447 DKDGLINKD	521 TLRESMELL	419 VVFVNQWSV	101 RAIHQALVQ
417 DTVVFVNQW	500 PAKMNFSYG	410 LGYHIPKDT	45 RQLRSAPPG
396 PVTIPHATT	495 ANPNEPAKM	366 RDRLPCM GD	41 RQRRRQLRS
388 AMRFSSFPV	493 FRANPNEPA	296 FILSAEKKA	10 PWPLNPLSI
347 TRYPDVQTR	486 ILAHQCDFR	285 PGAAPRDMM	505 FSYGLTIKP
340 QWLLLLFTR	464 SVGKRRRCIG	268 FSNFILDKF	412 YHIPKDTVV
323 TITDIFGAS	461 MIFSVGKRR	237 AGSLVDVMP	406 NTSVLGYHI
299 SAEKKAAGD	435 PNPENFDPA	185 SADGAFLDP	314 RLDLENVPA
294 DAFILSAEK	431 PLKWPNPEN	162 SRQVLEGHV	266 RNFSNFILD
291 DMMDAFILS	423 NQWSVNHDQ	156 FTRQPRSRQ	264 LNRNFSNFI
286 GAAPRDMMD	418 TVVFVNQWS	135 GHYSEHWKV	233 RTVGAGSLV
248 QYFPNPVRT	405 ANTSLVGYH	105 QALVQQGSA	154 NFFTRQPRS
229 EEFGRTVGA	389 MRFSSFPV	98 NGERAIHQ	146 RAAHSMMRN
226 SHNEEFGRT	377 NLPYVLAFL	71 HLSFARLAR	38 RLLRQRRRQ
203 NVMSAVCFG	375 QPNLPYVLA	13 LNPLSIQQT	532 AVQNLQAKE

198 VVAVANVMS	362 QVVGRDRLP	523 RESMELLD S	523 RESMELLD S
197 TVVAVANVM	361 DQVVGRDRL	509 LTIKPKSFK	507 YGLTIKPKS
195 PLTVVAVAN	360 LDQVVGRDR	469 RCIGEELSK	491 CDFRANPNE
185 SADGAFLDP	352 VQTRVQAE L	445 FLDKDG LIN	466 GKRR CIGEE
151 MMRNFFTRQ	323 TITDIFGAS	433 KWP NPENFD	419 VVFNQWSV
132 MAFGHYSEH	306 GDSHGGGAR	392 SSFVPVTIP	397 VTIPHATTA
112 SAFADRP AF	296 FILSAEKKA	388 AMRFSSFVP	392 SSFVPVTIP
90 GSCPIVVLN	295 AFILSAEKK	363 VVGRDRLPC	390 RFSSFVPVT
72 LSFARLARR	285 PGAAPRDMM	358 AELDQVVGR	366 RDRLPCM GD
70 AHL SFARLA	257 VFREFEQLN	282 SLRPGAAPR	355 RVQAE LDQV
34 HVGQRLLRQ	256 TVREFEQL	247 LQYFPNPVR	329 GASQDTLST
30 LATVHVGQR	247 LQYFPNPVR	241 VDVMPWLQY	325 TDIFGASQD
20 QTTL LLLLS	217 DDPEFRELL	234 TVGAGSLVD	312 GARLDLENV
518 VNVTLRESM	208 VCFGCRYSH	186 ADGAFLDPR	311 GGARLDLEN
493 FRANPNEPA	207 AVCFGCRY S	165 VLEGHV LSE	278 RHCESLRPG
461 MIFSVGKRR	204 VMSAVCFG C	160 PRSRQVLEG	248 QYFPNPVRT
446 LDKDGLINK	200 AVANVMSAV	120 FASFRVVS G	245 PWLQYFPNP
441 DPARFLDKD	198 VVAVANVMS	114 FADRPAFAS	238 GSLVDVMPW
421 FVNQWSVNH	197 TVVAVANVM	63 AA AVGQAAH	139 EHWKVQRR A
403 TTANTSVLG	195 PLTVVAVAN	43 RRRQLRSAP	121 ASFRVVS GG
392 SSFVPVTIP	180 LLVRGSADG	41 RQRRRQLRS	117 RPAFASF RV
376 PNLPHYVLA F	179 ALLVRGSAD	33 VHVGQRLLR	90 GSCPIVVLN
375 QPNLPYVLA	173 EARELVALL	511 IKPKSFKVN	83 DVFQIRLGS
351 DVQTRVQAE	155 FFTRQPRSR	494 RANPNEPAK	82 GDVFQIRLG
317 LENVPATIT	151 MMRNFFTRQ	488 AHQCDFRAN	55 FAWPLIGNA
304 AAGDSHGGG	140 HWKVQRRAA	459 RVMIFSVGK	53 GPFAWPLIG
259 REF EQLNRN	138 SEHWKVQRR	440 FDPARFLDK	52 PGFPAWPLI
201 VANVMSAVC	124 RVVSGGRSM	431 PLKWP NPEN	48 RSAPP GPFA
143 VQRRAAHSM	119 AFASF RVVS	416 KDTVVFVNQ	21 TTL LLLLSV
121 ASFRVVS GG	112 SAFADRP AF	324 ITDIFGASQ	534 QNLQAKETC
115 ADRPAFASF	109 QQGS AFADR	306 GDSHGGGAR	527 EL LDSAVQN
98 NGERAIHQA	95 VVLNGERAI	303 KAAGDSHGG	526 MEL LDSAVQ
93 PIVVLNGER	78 ARRYGDVFQ	267 NFSNFILDK	512 KPKSFKVNV
92 CPIVVLNGE	77 LARRYGDVF	251 PNPVRTVFR	462 IFSVGKRR C
68 QAAHLSFAR	70 AHL SFARLA	231 FGRTVGAGS	416 KDTVVFVNQ
56 AWPLIGNAA	65 AVGQAAHLS	230 EFGRTVGAG	411 GYHIPKDTV
14 NPLSIQQT T	63 AA AVGQAAH	215 SHDDPEFRE	409 VLG YHIPKD
10 PWPLNPLSI	62 NAAAVGQAA	179 ALLVRGSAD	373 GDQPNLPYV
533 VQNLQAKET	57 WPLIGNAAA	176 ELVALLVRG	359 ELDQVVGRD
507 YGLTIKPKS	40 LRQRRRQLR	175 RELVALLVR	326 DIFGASQDT
480 LFLFISILA	25 LLLSVLATV	151 MMRNFFTRQ	322 ATITDIFGA
469 RCIGEELSK	23 LLL LLSVLA	130 RSMAFGHYS	302 KKAAGDSHG
466 GKRR CIGEE	15 PLSIQQTTL	102 AIHQALVQQ	286 GAAPRDMM D
395 VPVTIPHAT	531 SAVQNLQAK	101 RAIHQALVQ	255 RTVFREFEQ
313 ARLDLENVP	518 VNVTLRESM	96 VLNGERAIH	229 EEFGRTVGA
311 GGARLDLEN	513 PKSFKVNV T	90 GSCPIVVLN	184 GSADGAFLD
305 AGDSHGGGA	506 SYGLTIKPK	75 ARLARRYGD	176 ELVALLVRG
289 PRDMMDAFI	504 NFSYGLTIK	60 IGNAAAVGQ	164 QVLEGHVLS
268 FSNFILDKF	502 KMNFSYGLT	54 PFAWPLIGN	156 FTRQPRSRQ
238 GSLVDVMPW	496 NPNEPAKMN	26 LLSVLATVH	107 LVQQGSAFA
234 TVGAGSLVD	485 SILAHQCDF	7 PN DPWPLNP	102 AIHQALVQQ
208 VCFGCRYSH	473 EELSKMQLF	4 SLSPNDPWP	88 RLGSCPIVV
207 AVCFGCRY S	470 CIGEELSKM	3 TSLSPNDPW	58 PLIGNAAAV
206 SAVCFGCRY	462 IFSVGKRR C	532 AVQNLQAKE	57 WPLIGNAAA
186 ADGAFLDPR	455 DLTSRV MIF	529 LDSAVQNLQ	34 HVGQRLLRQ
175 RELVALLVR	454 KDLTSRVMI	527 EL LDSAVQN	25 LLLSVLATV
142 KVQRRAAHS	449 DGLINKDLT	516 FKVNVTLRE	24 LLL LSVLAT
138 SEHWKVQRR	444 RFLDKDGLI	505 FSYGLTIKP	23 LLL LLSVLA
119 AFASF RVVS	441 DPARFLDKD	504 NFSYGLTIK	14 NPLSIQQT T

114 FADRPAFAS	427 VNHDPLKWP	495 ANPNEPAKM	13 LNPLSIQQT
103 IHQALVQQG	422 VNQWSVNHD	492 DFRANPNEP	2 GTSLSPNDP
101 RAIHQALVQ	390 RFSSSFVPVT	486 ILAHQCDFR	516 FKVNVTLRE
91 SCPIVVLNG	388 AMRFSSSFVP	481 FLFISILAH	511 IKPKSFKVN
84 VFQIRLGSC	384 FLYEAMRFS	464 SVGKRRRCIG	510 TIKPKSFKV
77 LARRYGDVF	382 LAFLYEAMR	462 IFSVGKRRRC	487 LAHQCDFRA
65 AVGQAHL	381 VLAFLYEAM	456 LTRVMIFS	482 LFISILAHQ
50 APPGPFAPW	380 YVLAFLYEA	447 DKDGLINKD	480 LFLFISILA
11 WPLNPLSIQ	369 LPCMGDQPN	439 NFDPARFLD	452 INKDLTSRV
530 DSAVQNLQA	368 RLPCM GDQP	428 NHDPLKWP	430 DPLKWP
513 PKSFKVNV	356 VQAELDQVV	427 VNHDPLKWP	429 HDPLKWP
464 SVGKRRRCIG	348 RYFDVQTRV	415 PKD TVFVN	380 YVLAFLYEA
456 LTRVMIFS	345 LFTRYPDVQ	408 SVLGYHIPK	368 RLPCM GDQP
427 VNHDPLKWP	343 LLLFTRYPD	404 TANTSVLGY	357 QAELDQVVG
422 VNQWSVNHD	332 QDTLSTALQ	403 TTANTSVLG	350 PDVQTRVQA
410 LGYHIPKDT	325 TDIFGASQD	398 TIPHATTAN	333 DTLSTALQW
393 SFVPVTIPH	313 ARDLLENVP	393 SFVPVTIPH	315 LDLENVPAT
386 YEAMRFSSSF	310 GGGARLDLE	379 PYVLAFLYE	308 SHGGGARLD
363 VVGRDRLPC	302 KKAAGDSHG	364 VGRDRLPCM	303 KAAGDSHG
362 QVVGDRDLP	270 NFILDKFLR	359 ELDQVVGRD	299 SAEKKAAGD
333 DTLSTALQW	269 SNFILDKFL	357 QAELDQVVG	292 MMDAFILSA
308 SHGGGARLD	261 FEQLNRNFS	318 ENVPATITD	274 DKFLRHCS
295 AFILSAEKK	259 REFEQLNRN	313 ARDLLENVP	237 AGSLVDVMP
293 MDAFILSAE	254 VRTVFREFE	311 GGARLDLEN	235 VGAGSLVDV
279 HCESLRPGA	244 MPWLQYFPN	308 SHGGGARLD	234 TVGAGSLVD
278 RHCESLRPG	236 GAGSLVDVM	304 AAGDSHGGG	228 NEEFGRTVG
267 NFSNFILDK	235 VGAGSLVDV	302 KKAAGDSHG	196 LTVAVANV
240 LVDVMPWLQ	232 GRTVGAGSL	301 EKKAAGDSH	191 LDPRPLTVV
184 GSADGAFLD	223 ELLSHNEEF	300 AEKKAAGDS	189 AFLDPRPLT
171 LSEARELVA	210 FGCRYSHDD	298 LSAEKKAAG	187 DGAFLDPRP
156 FTRQPRSRQ	201 VANVMSAVC	283 LRPGAAPRD	180 LLVRGSADG
147 AAHSMMRNF	199 VAVANVMSA	272 ILDKFLRHC	178 VALLVRGSA
146 RAAHSMMRN	191 LDPRPLTVV	271 FILDKFLRH	165 VLEGHVLSE
111 GSAFADRPA	172 SEARELVAL	236 GAGSLVDVM	125 VVSGGRSMA
83 DVFQIRLGS	166 LEGHVLSEA	228 NEEFGRTVG	118 PAFASFRVV
75 ARLARRYGD	163 RQVLEGHVL	224 LLSHNEEFG	105 QALVQQGSA
60 IGNAAVVGQ	162 SRQVLEGHV	220 EFRELLSHN	94 IVVLNGERA
35 VGQRLLRQR	159 QPRSRQVLE	208 VCFGCRYSH	92 CPIVVLNGE
6 SPNDPWPLN	158 RQPRSRQVL	204 VMSAVCFG	91 SCPIVVLNG
2 GTSLSPNDP	148 AHSMRNFF	203 NVMSAVCFG	67 GQAAHLSFA
523 RESMELDS	139 EHWKVQRRRA	198 VVAVANVMS	61 GNAAVVGQA
515 SFKVNVTLR	135 GHYSEHWKV	195 PLTVVAVAN	50 APPGPFAPW
506 SYGLTIKPK	133 AFGHYSEHW	161 RSRQVLEGH	12 PLNPLSIQ
504 NFSYGLTIK	127 SGGRSMAFG	153 RNFFTRQPR	11 WPLNPLSIQ
475 LSKMQLFLF	123 FRVVS GGRS	145 RRAAHSMR	1 MGTSLSPND
449 DGLINKDLT	120 FASFRVVSF	144 QRRAAHSM	529 LDSAVQNLQ
432 LKWPNPENF	108 VQQGSAFAD	141 WKVQRRRAH	525 SMELLSAV
405 ANT SVLGYH	107 LVQQGSAFA	136 HYSEHWKVQ	524 ESMELLSA
357 QAELDQVVG	105 QALVQQGSA	133 AFGHYSEHW	517 KVNVTRES
320 VPATITDIF	104 HQALVQQGS	129 GRSMAGHY	513 PKSFKVNV
310 GGGARLDLE	100 ERAIHQALV	127 SGGRSMAFG	484 ISILAHQCD
302 KKAAGDSHG	92 CPIVVLNGE	121 ASFRVVS	477 KMQLFLFIS
283 LRPGAAPRD	89 LGSCPIVVL	110 QGSAFADRP	471 IGEELSKMQ
280 CESLRPGAA	86 QIRLGSCPI	109 QQGSAFADR	457 TSRVMIFS
255 RTVFREFEQ	85 FQIRLGSCP	108 VQQGSAFAD	433 KWPNPENFD
222 RELLSHNEE	79 RRYGDVFI	103 IHQALVQQG	431 PLKWP
219 PEFRELLSH	75 ARLARRYGD	91 SCPIVVLNG	428 NHDPLKWP
161 RSRQVLEGH	74 FARLARRYG	83 DVFQIRLGS	417 DTVFVNQW
149 HSMRNFF	58 PLIGNAAV	80 RYGDVFI	407 TSVLGYHIP

78	ARRYGDVFO	56	AWPLIGNAA	74	FARLARRYG	401	HATTANTSV
74	FARLARRYG	52	PGPFAWPLI	65	AVGQAAHLS	399	IPHATTANT
73	SFARLARRY	42	QRRRQLRSA	59	LIGNAAAVG	394	FVPVTIPHA
54	PFAWPLIGN	39	LLRQRRRQL	46	QLRSAPPGP	388	AMRFSSFPV
52	PGPFAWPLI	26	LLSVLATVH	45	RQLRSAPPG	362	QVVGRDRLP
534	QNLQAKETC	22	TLLLLLSVL	44	RRQLRSAPP	356	VQAELDQVV
526	MELLDASVQ	535	NLQAKETCQ	36	GQRLLRQRR	346	FTRYPDVQT
516	FKVNVTLRE	527	ELLDASVQN	34	HVGQRLLRQ	344	LLFTRYPDV
489	HQCDFRANP	526	MELLDASVQ	29	VLATVHVVG	339	LQWLLLLFT
484	ISILAHQCD	519	NVTLRESME	28	SVLATVHVG	330	ASQDTLSTA
462	IFSVGKRRRC	508	GLTIKPKSF	535	NLQAKETCQ	318	ENVPATITD
453	NKDLTSRVM	501	AKMNFSYGL	526	MELLDASVQ	317	LENVPATIT
378	LPYVLAFLY	491	CDFRANPNE	522	LRESMELL	310	GGGARLDLE
369	LPCM GDQPN	489	HQCDFRANP	515	SFKVNVTLR	300	AEKKAAGDS
353	QTRVQAELD	483	FISILAHQC	506	SYGLTIKPK	298	LSAEKKAAG
349	YPDVQTRVQ	479	QLFLFISIL	498	NEPAKMNFS	296	FILSAEKKA
306	GDSHG G GAR	467	KRRCIGEEL	490	QCDFRANPN	281	ESLRPGAAP
288	APRDMMDAF	448	KDGLINKDL	489	HQCDFRANP	272	ILDKFLRHC
285	PGAAPRDM	443	ARFLDKDGL	483	FISILAHQC	262	EQLNRNFSN
284	RPGAAPRDM	438	ENFDPARFL	466	GKRRCIGEE	252	NPVRTVFRE
257	VFREFEQLN	433	KWPNPENFD	458	SRVMIFS,SVG	243	VMPWLQYFP
252	NPVRTVFRE	421	FVNQWSVNH	453	NKDLTSRVM	226	SHNEEFGR
250	FPNPVRTVF	419	VVFNQWSV	451	LINKDLTSR	220	EFRELLSHN
247	LQYFPNPVR	414	IPKDTVVVF	450	GLINKDLTS	211	GCRYSHDDP
237	AGSLVDVMP	413	HIPKDTVVF	442	PARFLDKDG	199	VAVANVMSA
231	FGRTVGAGS	411	GYHIPKDTV	426	SVNHDPLKW	192	DPRPLTVVA
220	EFRELLSHN	401	HATTANTSV	421	FVNQWSVNH	181	LVRGSADGA
215	SHDDPEFRE	396	PVTIPHATT	409	VLGYHIPKD	179	ALLVRGSAD
202	ANVMSAVCF	395	VPVTIPHAT	405	ANTSVLGYH	166	LEGHVLSEA
160	PRSRQVLEG	394	FVPVTIPHA	385	LYEAMRFSS	151	MMRNFFTRQ
144	QRRAAHSM	383	AFLYEAMRF	381	VLAFLYEAM	142	KVQRRAAHS
140	HWKVQRRAA	374	DQPNLPYVL	368	RLPCM GDQP	131	SMAFGHYSE
127	SGGRSMAFG	370	PCM GDQPNL	362	QVVGRDRLP	130	RSMAFGHYS
126	VSGGRSMAF	366	RDRLP CMGD	354	TRVQAELDQ	111	GSAFADRPA
108	VQGSASFAD	364	VGRDRLPCM	353	QTRVQAELD	108	VQGSASFAD
97	LNGERAIHQ	351	DVQTRVQAE	351	DVQTRVQAE	104	HQALVQQGS
85	FQIRLGSCP	350	PDVQTRVQA	347	TRYPDVQTR	103	IHQALVQQG
82	GDVFQIRLG	344	LLFTRYPDV	343	LLLTRYPD	98	NGERAIHQA
66	VGQAAHLSF	342	LLLLFTRY	341	WLLLLFTRY	85	FQIRLGSCP
33	VHVGQRLLR	334	TLSTALQW	333	DTLSTALQW	76	RLARRYGDV
9	DPWPLNPLS	326	DIFGASQDT	332	QDTLSTALQ	70	AHLSFARLA
529	LDSAVQNLQ	320	VPATITDIF	328	FGASQDTLS	65	AVGQAAHLS
519	NVTLRESME	317	LENVPATIT	323	TITDIFGAS	56	AWPLIGNAA
496	NPNEPAKM	315	LDLENVPAT	310	GGGARLDLE	28	SVLATVHVG
488	AHQCDFRAN	304	AAGDSHG G G	299	SAEKKAAGD	20	QTLLLLLS
471	IGEELSKMQ	303	KAAGDSHG G	295	AFILSAEKK	9	DPWPLNPLS
435	PNPENFDPA	301	EKKAAGDSH	293	MDAFILSAE	7	PNDPWPLNP
434	WPNPENFD	300	AEKKAAGDS	291	DMMDAFILS	3	TSLSPNDPW
433	KWPNPENFD	297	ILSAEKKAA	286	GAAPRDMMD	535	NLQAKETCQ
428	NHDPLKWP	288	APRDMMDAF	278	RHCESLRPG	533	VQNLQAKET
418	TVVFNQWS	287	AAPRDMMDA	277	LRHCESLRP	530	DSAVQNLQA
407	TSVLGYHIP	283	LRPGAAPRD	276	FLRHCESLR	502	KMNFSYGLT
385	LYEAMRFSS	273	LDKFLRHCE	266	RNFSNFILD	496	NPNEPAKM
383	AFLYEAMRF	265	NRNFSNFIL	261	FEQLNRNFS	489	HQCDFRANP
367	DRLPCM GDQ	262	EQLNRNFSN	258	FREFEQLNR	483	FISILAHQC
350	PDVQTRVQA	252	NPVRTVFRE	257	VFREFEQLN	449	DGLINKDLT
332	QDTLSTALQ	246	WLQYFPNPV	254	VRTVFREFE	445	FLDKDGLIN
328	FGASQDTLS	243	VMPWLQYFP	245	PWLQYFPNP	441	DPARFLDKD
325	TDIFGASQD	230	EFGRTVGAG	238	GSLVDVMPW	434	WPNPENFD

318 ENVPATITD
281 ESLRPGAAP
277 LRHCESLRP
253 PVRTVFREF
241 VDVMPWLQY
225 LSHNEEFGR
214 YSHDDPEFR
213 RYSHDDPEF
210 FGCRYSHDD
168 GHVLSEARE
152 MRNFFTRQP
148 AHSMMRNFF
141 WKVQRRRAH
137 YSEHWKVQR
133 AFGHYSEHW
130 RSMAFGHYS
122 SFRVVS GGR
104 HQALVQQGS
53 GPFAPWPLIG
47 LRSAPPGPF
45 RQLRSAPPG
3 TSLSPNDPW
522 LRESMELLD
498 NEPAKMNFS
492 DFRANPNP
491 CDFRANPNE
468 RRCIGEELS
458 SRVMIFSVG
440 FDPARFLDK
439 NFDPARFLD
436 NPENFDPAR
430 DPLKWPNE
429 HDPLKWPNP
423 NQWSVNHDP
416 KDTVVFVNQ
400 PHATTANTS
372 MGDQPNLPY
366 RDRLPCM GD
365 LDQVVGDR
360 LDQVVGDR
345 LFTRYPDVQ
274 DKFLRHCE

273 LDKFLRHCE
270 NFILDKFLR
261 FEQLNRNFS
230 EFGRTVGAG
221 FRELLSHNE
205 MSAVCFGCR
187 DGAFLDPRP
182 VRGSADGAF
159 QPRSRQVLE

155 FFTRQPRSR
154 NFFTRQPRS
145 RRAAHSM MR

139 EHWKVQRRRA
128 GGRSMAFGH

229 EEFGRTVGA
224 LLSHNEEFGR
203 NVMSAVCFG
202 ANVMSAVCF
193 PRPLTVVAV
186 ADGAFLDPR
183 RGSADGAFL
182 VRGSADGAF
181 LVRGSADGA
177 LVALLVRGS
176 ELVALLVRG
153 RNFFTRQPR
147 AAHSMMRNFF
145 RRAAHSM MR
144 QRRRAHSM
143 VQRRRAHSM
141 WKVQRRRAH
136 HYSEHWKVQ
134 FGHYSEHWK
132 MAFGHYSEH
113 AFADRPAPA
103 IHQALVQQG
102 AIHQALVQQ
94 IVVLNGERA
93 PIVVLNGER
87 IRLGSCPIV
84 VFQIRLGSC
76 RLARRYGDV
61 GNAAAVGQA
59 LIGNAAAVG
47 LRSAPPGPF
46 QLSAPPGP
43 RRRQLRSAP
36 GQRLLRQRR
35 VGQRLLRQR
30 LATVHVQGR
11 WPLNPLSIQ
8 NDPWPLNPL

HLA-A1 Decamers

Pos 1234567890

240 LVDVMPWLQY
403 TTANTSVLGY
439 NFDPARFLDK
371 CMGDQPNLPY
205 MSAVCFGCRY
72 LSFARLARRY
377 NLPYVLAFLY
340 QWLLLLFTRY
174 ARELVALLVR

128 GGRSMAFGHY
216 HDDPEFRELL
190 FLDPRPLTVV

137 YSEHWKVQRR
522 LRESMELLD

219 PEFRELLSH
211 GCRYSHDDP
207 AVCFGCRY
205 MSAVCFGCR
201 VANVMSAVC
197 TVVAVANVM
187 DGAFLDPRP
177 LVALLVRGS
167 EGHVLSEAR
164 QVLEGHVLS
150 SMRNFFTR
146 RAAHSMMRN
143 VQRRRAHSM
142 KVQRRRAHS
137 YSEHWKVQR
132 MAFGHYSEH
128 GGRSMAFGH
124 RVVSGGRSM
122 SFRVVS GGR
116 DRPAFASFR
72 LSFARLARR
68 QAAHLSFAR
49 SAPPGPFAW
38 RLLRQRRRQ
20 QTTL LLLLS
2 GTSLSPNDP
531 SAVQNLQAK
518 VNVTLRESM
517 KVNVTLRES
507 YGLTIKPKS
500 PAKMNFSYG
491 CDFRANPNE
484 ISILAHQCD
482 LFISILAHQ
477 KMQLFLFIS
471 IGEELSKMQ
470 CIGEELSKM
468 RRCIGEELS
461 MIFSVGKRR
460 VMIFSVGKR
429 HDPLKWPNP
425 WSVNHDPK

422 VNQWSVNHDP
420 VVFNQWSVN
417 DTVVFVNQW
400 PHATTANTS
384 FLYEAMRFS
382 LAFLYEAMR
371 CMGDQPNLP
367 DRLPCM GDQ
365 GRDLPCM GD

360 LDQVVGDR
345 LFTRYPDVQ
342 LLLLFTRY

321 PATITDIFG
294 DAFILSAEK

426 SVNHDPLKW
422 VNQWSVNHDP
420 VVFNQWSVN
418 TVVFVNQWS
415 PKDTVVFVN
414 IPKDTVVFV
410 LGYHIPKDT
400 PHATTANTS
396 PVTIPHATT
384 FLYEAMRFS
379 PYVLAFLYE
375 QPNLPYVLA
369 LPCMGDQPN
343 LLLFTRYPD
342 LLLLFTRY
332 QDTLSTALQ
328 FGASQDTLS
324 ITDIFGASQ
297 ILSAEKKA
293 MDAFILSAE
249 YFPNPVRTV
215 SHDDPEFRE
207 AVCFGCRY
201 VANVMSAVC
200 AVANVMSAV
195 PLTVVAVAN
190 FLDPRPLTV
185 SADGAFLDP
177 LVALLVRGS
159 QPRSRQVLE
120 FASFRVVS
119 AFASFRVVS
110 QGSADFADRP
97 LNGERAIHQ
60 IGNAAAVGQ
59 LIGNAAAVG
54 PFAWPLIGN
49 SAPPGPFAW
27 LSVLATVHV
4 SLSPNDPWP
519 NVTLRESME
498 NEPAKMNFS

492 DFRANPNP
490 QCDFRANPN
464 SVGKRRRCIG
456 LTRVMIFS
442 PARFLDKDG
427 VNHDPLKWP
423 NQWSVNHDP
403 TTANTSVLG
398 TIPHATTAN

395 VPVTIPHAT
387 EAMRFSFV
321 PATITDIFG

304 AAGDSHGGG
287 AAPRDMMDA

109 QQGSADFADR
44 RRQLRSAPP
43 RRRQLRSAP
40 LRQRRRQLR
37 QRLLRQRRR
36 GQRLLRQRR
511 IKPKSFKVN
499 EPAKMNFSY
465 VGKRRRCIGE
425 WSVNHDPLK
420 VFNQWSVN
415 PKDTVVFN
354 TRVQAELDQ
300 AEKKAAGDS
266 RNFSNFILD
262 EQLNRNFSN
254 VRTVFREFE
251 PNPVRTVFR
245 PWLQYFPNP
244 MPWLQYFPN
212 CRYSHDDPE
136 HYSEHWKVQ
134 FGHYSEHWK
129 GRSMAGHY
123 FRVVS GGRS
110 QGSADFADRP
80 RYGDVVFQIR

41 RQRRRQLRS

1 MGTSLSPND
437 PENFDPARF
167 EGHVLSEAR
497 PNEPAKMNF

379 PYVLAFLYE
301 EKKAAGDSH
218 DPEFRELLS
260 EFEQLNRNF

HLA-A*0201 Decamers

Pos 1234567890
24 LLLLSVLATV
190 FLDPRPLTVV
88 RLGSCPIVVL
17 SIQQTLLLLL
527 ELLDSAVQNL
413 HIPKDTVVFN
343 LLLFTRYPDV
26 LLSVLATVHV
23 LLLLSVLAT
4 SLSPNDPWPL
336 STALQWLLLL
456 LTSRVMIFSV
326 DIFGASQDTL
195 PLTVVAVANV

498 NEPAKMNFSY
445 FLDKDGLINK
336 STALQWLLLL
324 ITDIFGASQD
218 DPEFRELLSH
215 SHDDPEFREL
90 GSCPIVVLNG
497 PNEPAKMNFS
428 NHDPLKWPNP
331 SQDTLSTALQ
233 RTVGAGSLVD
171 LSEARELVAL
114 FADRPAFASF
81 YGDVVFQIRLG
7 PNDPWPLNPL
528 LLDSAVQNLQ
525 SMELLDSAVQ
475 LSKMQLFLFI
415 PKDTVVFNQ
385 LYEAMRFSS
349 YPDVQTRVQA
185 SADGAFLDPR
184 GSADGAFLDP
165 VLEGHVLSA
472 GEELSKMQLF
453 NKDLTSRVM
447 DKDGLINKDL

425 WSVNHDPLKW

359 ELDQVVGRDR
353 QTRVQAELDQ
335 LSTALQWLLL
314 RLDLENVPAT

305 AGDSHGGGAR
299 SAEKKAAGDS
272 ILDKFLRHCE
227 HNEEFGRTVG
20 QTTL LLLLLSV

16 LSIQQTTL L

490 QCDFRANPNE
397 VTIPHATTAN
357 QAELDQVVGR
316 DLENVPATIT
260 EFEQLNRNFS
258 FREFEQLNRN
221 FRELLSHNEE
471 IGEELSKMQL
436 NPENFDPARF
392 SSFVPVTIPH
372 MGDQPNLPYV
365 GRDRLPCM GD
322 ATITDIFGAS
308 SHGGGARLDL
292 MMDAFILSAE
289 PRDMMDAFIL

273 LDKFLRHCE
262 EQLNRNFSN
259 REFEQLNRN
255 RTVFREFEQ
243 VMPWLQYFP
240 LVDVMPWLQ
222 RELLSHNEE
214 YSHDDPEFR
212 CRYSHDDPE
209 CFGCRYSHD
206 SAVCFGCRY
184 GSADGAFLD
180 LLVRGSADG
168 GHVLSEARE
154 NFFTRQPRS
152 MRNFFTRQP
138 SEHWKVQRR
131 SMAFGHYSE
123 FRVVS GGRS
104 HQALVQQGS
97 LINGERAIHQ
85 FQIRLGSCP
73 SFARLARRY
40 LRQRRRQLR
30 LATVHVQGR
12 PLNPLSIQQ
1 MGTSLSPND

HLA-B*0702 Decamers

Pos 1234567890
50 APPGPFAWPL

192 DPRPLTVVAV
288 APRDMMDAFI
369 LPCMGDQPNL
14 NPLSIQQTTL
375 QPNLPYVLAF

349 YPDVQTRVQA

284 RPGAAPRDMM
117 RPAFASFRRV
512 KPFSFKVNV
434 WPNPENFDPA
51 PPGPFAWPLI
9 DPWPLNPLSI
57 WPLIGNAAAV
436 NPENFDPARF
395 VPVTI PHATT
252 NPVRTVFREF
496 NPNEPAKMNF
308 SHGGGARLDL
250 FPNPVRTVFR
159 QPRSRQVLEG
88 RLGSCPIVVL
513 PKFSFKVNVTL

279 HCESLRPGA
261 FEQLNRNFS
231 FGRTVGAGS
227 HNEEFGRTV
198 VVAVANVMS
171 LSEARELVA
136 HYSEHWKVQ
133 AFGHYSEHW
127 SGRSMAFG
114 FADRPAFAS
113 AFADRPAF
84 VFQIRLGSC
29 VLATVHVQ
6 SPNDPWPLN
500 PAKMNFSYG
488 AHQCDFRAN
465 VGKRRRCIGE
439 NFDPARFLD
435 PNPENFDPA
385 LYEAMRFSS
371 CMGDQPNLP
363 VVGRDR LPC
353 QTRVQAELD
351 DVQTRVQAE
349 YPDVQTRVQ
345 LFTRYPDVQ
323 TITDIFGAS

305 AGDSHGGGA

291 DMMDAFILS
280 CESLRPGAA
273 LDKFLRHCE
257 VFREFEQLN

246 WLQYFPNPV
244 MPWLQYFPN
240 LVDVMPWLQ
230 EFGRTVGAG
218 DPEFRELLS

210 FGCERYSHDD

209 CFGCRYSHD
204 VMSAVCFG
203 NVMSAVCFG
170 VLSEARELV
149 HSMRNFFFT
74 FARLARRYG
62 NAAAVGQAA
46 QLSAPP GP

HLA-B8 Octamers

Pos 12345678
159 QPRSRQVL
521 TLRESMEL
510 TIKPKSFK
218 DPEFRELL

165 VLEGHVLSSEA	279 HCESLRPGAA	499 EPAKMNFSYG	173 EARELVAL
38 RLLRQRRRQL	228 NEEFGRTVGA	473 EELSKMQLFL	515 SFKVNVTL
451 LINKDLTSRV	98 NGERAIHQAL	388 AMRFSSFPVP	414 IPKDTVVF
388 AMRFSSFPVP	17 SIQQTTLTLL	330 ASQDTLSTAL	276 FLRHCESL
338 ALQWLLLLFT	9 DPWPLNPLSI	194 RPLTVVAVAN	473 EELSKMQL
509 LTIKPKSFKV	521 TLRESMELL	171 LSEARELVAL	475 LSKMQLFL
502 KMNFSYGLTI	520 VTLRESMELL	63 AAAGVQAAHL	455 DLTSRVMI
334 TLSTALQWLL	402 ATTANTSVLG	15 PLSIQQTTL	444 RFLDKDGL
314 RLDLENVPAT	378 LPYVLAFLYE	4 SLSPNDPWPL	39 LLRQRRRQ
291 DMMDAFILSA	290 RDMMDAFILS	447 DKDGLINKDL	465 VGKRRRCIG
263 QLNRNFSNFI	270 NFILDKFLRH	414 IPKDTVVFVN	310 GGGARLDL
234 TVGAGSLVDV	265 NRNFSNFILD	378 LPYVLAFLYE	257 VFREFEQL
172 SEARELVALL	255 RTVFREFEQL	376 PNLPYVLAFL	170 VLSEAREL
63 AAAGVQAAHL	170 VLSEARELVA	336 STALQWLLLL	362 QVVGRDRL
21 TTTLLLLLSVL	49 SAPPGPFAWP	335 LSTALQWLLL	40 LRQRRRQL
20 QTTLTLLLSV	32 TVHVGQRLLR	306 GDSHGGGARL	6 SPNDPWPL
477 KMQLFLFISI	31 ATVHVGQRLL	216 HDDPEFRELL	508 GLTIKPKS
450 GLINKDLTSR	515 SFKVNVTLRE	182 VRGSADGAFL	450 GLINKDLT
333 DTLSTALQWL	510 TIKPKSFKVN	172 SEARELVALL	378 LPYVLAFL
248 QYFPNPVRTV	509 LTIKPKSFKV	157 TRQPRSRQVL	375 QPNLPYVL
86 QIRLGSCPIV	457 TSRVMIFSOG	68 QAAHLSFARL	353 QTRVQAEI
486 ILAHQCDFRA	407 TSVLGYHIPK	18 IQQTTLTLLL	23 LLLLLSVL
481 FLFISILAHQ	362 QVVGRDRLPC	16 LSIQQTTLTLL	535 NLQAKETC
315 LDLENVPATI	346 FTRYPDVQTR	7 PNDPWPLNPL	512 KPKSFKVN
192 DPRPLTVVAV	338 ALQWLLLLFT	527 ELDSAVQNL	498 NEPAKMNF
189 AFLDPRPLTV	337 TALQWLLLLF	466 GKRRRCIGEL	464 SVGKRRCI
171 LSEARELVAL	276 FLRHCESLRP	442 PARFLDKDGL	431 PLKWPNPEN
170 VLSEARELVA	217 DDPEFRELLS	430 DPLKWPNPEN	338 ALQWLLLL
106 ALVQQGSFAF	173 EARELVALLV	401 HATTANTSVL	299 SAEKKAAG
68 QAAHLSFARL	70 AHLSEARLAR	399 IPHATTANTS	17 SIQQTTLTLL
22 TLLLLLSVLA	48 RSAPPGPFAW	373 GDQPNLPYVL	9 DPWPLNPL
12 PLNPLSIQQT	33 VHVVGQRLLRQ	334 TLSTALQWLL	384 FLYEAMRF
520 VTLRESMELL	23 LLLLLSVLAT	326 DIFGASQDTL	364 VGRDRLPC
408 SVLGYHIPKD	19 QQTTLTLLLS	320 VPATITDIFG	271 FILDKFLR
376 PNLPYVLAFL	18 IQQTTLTLLL	264 LNRNFSNFIL	251 PNPVRTVF
351 DVQTRVQAEI	6 SPNDPWPLNP	255 RTVFREFEQL	190 FLDPRPLT
311 GGARLDLENV	529 LDSAVQNLOA	244 MPWLQYFPNP	179 ALLVRGSA
226 SHNEEFGRTV	514 KSFKVNVTLR	231 FGRTVGAGSL	149 HSMMRNFF
198 VVAVANVMSA	502 KMNFSYGLTI	218 DPEFRELLSH	500 PAKMNFSY
180 LLVRGSADGA	479 QLFLFISILA	215 SHDDPEFREL	474 ELSKMQLF
29 VLATVHVQGQR	477 KMQLFLFISI	187 DGAFLDPRPL	344 LLFTRYPD
18 IQQTTLTLLL	463 FSVGKRRRCIG	80 RYGDVVFQIRL	337 TALQWLLL
15 PLSIQQTTLTLL	444 RFLDKDGLIN	38 RLLRQRRRQL	282 SLRPGAAP
384 FLYEAMRFSS	434 WPNPENFDPA	31 ATVHVGQRLL	113 AFADRPAP
271 FILDKFLRHC	417 DTVVFVNQWS	17 SIQQTTLTLLL	76 RLARRYGD
199 VAVANVMSAV	412 YHIPKDTVVF	6 SPNDPWPLNP	41 RQRRRQLR
179 ALLVRGSADG	375 QPNLPYVLAFL	529 LDSAVQNLOA	486 ILAHQCDF
169 HVLSEARELV	328 FGASQDTLST	471 IGEELSKMQL	479 QLFLFISI
87 IRLGSCPIVV	307 DSHGGGARLD	441 DPARFLDKDG	445 FLDKDGLI
31 ATVHVGQRLL	282 SLRPGAAPRD	437 PENFDPARFL	377 NLPYVLAFL

519 NVTLRESMEL
494 RANPNEPAKM

479 QLFLFISILA
478 MQLFLFISIL
445 FLDKDGLINK
418 TVVFNQWSV
410 LGYHIPKDTV
372 MGDQPNLPYV
342 LLLLFTRYPD
329 GASQDTLSTA
308 SHGGGARLDL

297 LSAEKKAAAG

296 FILSAEKKAA

282 SLRPGAAPRD
215 SHDDPEFREL
164 QVLEGHVLSE
156 FTRQPRSRQV
94 IVVLNGERAI

71 HLSFARLARR
57 WPLIGNAAAV
30 LATVHVQGRL

16 LSIQQTLLL
511 IKPKSFKVNV
469 RCIGEELSKM
398 TIPHATTANT
386 YEAMRFSSSFV
381 VLAFLYEAMR
373 GDQPNLPYVL
363 VVGRDRLPCM
355 RVQAELEDQV
354 TRVQAELEDQV
330 ASQDTLSTAL
238 GSLVDVMPWL
177 LVALLVRGSA

173 EARELVALLV
102 AIHQALVQQG
96 VLNGERAIHQ
75 ARLARRYGDV
55 FAWPLIGNAA

50 APPGPFAPWL
25 LLSVLATVHV
14 NPLSIQQTLL
7 PNDPWPLNPL
528 LLSAVQNLQ
521 TLRESMELLD

471 IGEELSKMQL
466 GKRRRCIGEEL

409 VLGYPHIPKDT

257 VFREFEQLNR
225 LSHNEEFGR

196 LTVVAVANVM
189 AFLDPRPLTV
164 QVLEGHVLSE
159 QPRSRQVLEG
156 FTRQPRSRQV
149 HSMNRNFFTR
100 ERAIHQALVQ
96 VLNGERAIHQ
82 GDVFQIRLGS

65 AVGQAAHLSF

21 TTLLLLLSVL

4 SLSPNDPWPL
2 GTSLSNDPW
505 FSYGLTIKPK
504 NFSYGLTIKPK
494 RANPNEPAKM

480 LFLFISILAH
473 EELSKMQLFL
468 RRCIGEELSK

464 SVGKRRRCIGE
456 LTRVMIFSV
449 DGLINKDLTS
406 NTSVLGYHIP
393 SFVPVTIPHA
391 FSSFVPVTIP
333 DTLSTALQWL
332 QDTLSTALQW
310 GGGARLDLEN
291 DMMDAFILSA
266 RNFSNFILDK
214 YSHDDPEFRE
157 TRQPRSRQVL

126 VSGGRSMAFG
87 IRLGSCPIVV
55 FAWPLIGNAA
52 PGPFAPWLIG
51 PPGPFAPWLI

40 LRQRRRQLRS
27 LSVLATVHV
5 LSPNDPWPLN
455 DLTSRVMIFS
408 SVLGYPHIPKD
373 GDQPNLPYVL

367 DRLPCM GDQP
330 ASQDTLSTAL

320 VPATITDIFG

423 NQWSVNHDPL
413 HIPKDTVVVF

412 YHIPKDTVVVF
390 RFSSFVPVTI
360 LDQVVGRDRL
351 DVQTRVQAE
338 ALQWLLLLFT
314 RLDLENVPAT
313 ARLDLENVPA
289 PRDMMDAFIL
268 FSNFILDKFL

238 GSLVDVMPWL

235 VGAGSLVDVM

181 LVRGSADGAF
173 EARELVALLV
170 VLSEARELVA
162 SRQVLEGHVL
148 AHSMNRNFFT

125 VVSGGRSMAF
98 NGERAIHQAL
78 ARRYGDVFQI

65 AVGQAAHLSF
53 GPFAPWLIGN
47 LRSAPPGPFA
26 LLSVLATVHV
21 TTLLLLLSVL
520 VTLRESMELL
519 NVTLRESMEL
511 IKPKSFKVNV
500 PAKMNFSYGL
492 DFRANPNEPA
478 MQLFLFISIL
475 LSKMQLFLFI
474 ELSKMQLFLF

462 IFSVGKRRCI
453 NKDLTSRVM
333 DTLSTALQWL
328 FGASQDTLST
274 DKFLRHCESL

234 TVGAGSLVDV
191 LDPRPLTVVA
190 FLDPRLPLTVV
189 AFLDPRPLTV
168 GHVLSEAREL
147 AAHSMNRNFF

139 EHWKVQRRAA
111 GSAFADRPAP

110 QGSFADRPAP

336 STALQWLL
320 VPATITDI

286 GAAPRDMM
120 FASFRVVS
96 VLNGERAI
78 ARRYGDVF
53 GPFAPWLI
429 HDPLKWP
387 EAMRFSSF
312 GARLDLEN
308 SHGGGARL

301 EKKAAGDS

298 LSAEKKAA

288 APRDMMDA
264 LNRNFSNF
224 LLSHNEEF
217 DDOPEFREL
192 DPRPLTVV

164 QVLEGHVL
140 HWKVQRRRA
138 SEHWKVQR

100 ERAIHQAL
74 FARLARRY
46 QLRSAPP
11 WPLNPLSI
463 FSVGKRRRC
452 INKDLTSR
332 QDTLSTAL
328 FGASQDTL
270 NFILDKFL
240 LVDVMPWL
184 GSADGAFL
174 ARELVALL
90 GSCPIVVL

86 QIRLGSC
82 GDVFQIRL
33 VHVQRRLL
32 TVHVQRRLL
20 QTLLLLLL

18 IQQTLLLL
529 LDSAVQNL
522 LRESMELL
513 PKSFKVNV
502 KMNFSYGL
480 LFLFISIL

468 RRCIGEEL
449 DGLINKDL

446 LDKDGLIN

401 HATTANTSVL	268 FSNFILDKFL	106 ALVQQGSAFA	442 PARFLDKD
393 SFVPVTIPHA	250 FPNPVRTVFR	99 GERAIHQALV	439 NFDPARFL
380 YVLAFLYEAM	248 QYFPNPVRTV	92 CPIVVLNGER	425 WSVNHDPL
369 LPCMGDQPNL	239 SLVDVMPWLQ	87 IRLGSCPIVV	412 YHIPKDTV
347 TRYPDVQTRV	192 DPRPLTVVAV	56 AWPLIGNAAA	403 TTANTSVL
344 LLFTRYPDVQ	172 SEARELVALL	30 LATVHVQGRL	371 CMGDQPNL
306 GDSHGGGARL	150 SMMRNFFTRQ	23 LLLLSVLAT	335 LSTALQWL
292 MMDAFILSAE	121 ASFRVVSGGR	11 WPLNPLSIQQ	321 PATITDIF
288 APRDMMDAFI	115 ADRPAFASF	524 ESMELLSAV	300 AEKKAAGD
286 GAAPRDMMDA	111 GSAFADRPFAF	523 RESMELLSA	291 DMMDAFIL
272 ILDKFLRHCE	108 VQQGSAFADR	502 KMNFSYGLTI	273 LDKFLRHC
255 RTVFREFEQL	12 PLNPLSIQQT	501 AKMNFSYGLT	266 RNFSNFIL
239 SLVDVMPWLQ	531 SAVQNLQAKE	494 RANPNEPAKM	262 EQLNRNFS
235 VGAGSLVDVM	530 DSAVQNLQAK	469 RCIGEELSKM	233 RTVGAGSL
231 FGRTVGAGSL	524 ESMELLSAV	389 MRFSSFVPVT	229 EEFGRTVG
224 LLSHNEEFGR	506 SYGLTIKPKS	355 RVQAEILDQVV	220 EFRELLSH
182 VRGSADGAFL	484 ISILAHQCDF	318 ENVPATITDI	189 AFLDPRPL
168 GHVLSEAREL	432 LKWPNPENFD	304 AAGDSHGGGA	97 LGERAIHQ
162 SRQVLEGHVL	388 AMRFSFVPV	291 DMMDAFILSA	77 LARRYGDV
131 SMAFGHYSEH	376 PNLPHYVLAFL	287 AAPRDMMDAF	70 AHLSEARL
112 SAFADRPAPA	347 TRYPDVQTRV	278 RHCESLRPGA	65 AVGQAAHL
99 GERAIHQALV	318 ENVPATITDI	249 YFPNPVRTVF	52 PGFAFWL
97 LGERAIHQ	317 LENVPATITD	228 NEEFGRTVGA	19 QQTLLLL
78 ARRYGDVFQI	298 LSAEKKAAGD	193 PRPLTVVAVA	16 LSIQQTTL
59 LIGNAAAVGQ	286 GAAPRDMMDA	161 RSRQVLEGHV	519 NVTLRESM
58 PLIGNAAAVG	281 ESLRPGAAPR	114 FADRPASF	440 FDPARFLD
9 DPWPLNPLSI	269 SNFILDKFLR	112 SAFADRPAPA	392 SSFVPVTI
517 KVNVTLRESM	249 YFPNPVRTVF	86 QIRLGSCPIV	280 CESLRPGA
500 PAKMNFSYGL	242 DVMPWLQYFF	76 RLARRYGDVF	274 DKFLRHCE
485 SILAHQCDFR	238 GSLVDVMPWL	75 ARLARRYGDV	126 VSGGRSMA
403 TTANTSVLGY	235 VGAGSLVDVM	61 GNAAAVGQAA	122 SFRVVSGG
390 RFSSFVPVTI	204 VMSAVCFGCR	60 IGNAAAVGQA	84 VFQIRLGS
360 LDQVVGRDRL	162 SRQVLEGHVL	46 QLSAPPGP	44 RRQLRSAP
341 WLLLLFTRYP	161 RSRQVLEGHV	41 RQRRRLRSLA	37 QRLLRQRR
335 LSTALQWLLL	130 RSMAFGHYSE	532 AVQNLQAKET	34 HVGQRLLR
323 TITDIFGASQ	117 RPAFASFRRV	517 KVNVTLRESM	527 ELLDSAVQ
316 DLENVPATIT	80 RYGDVFQIRL	486 ILAHQCDFRA	499 EPAKMNFS
304 AAGDSHGGGA	79 RRYGDVFQIR	477 KMQLFLFISI	496 NPNEPAKM
276 FLRHCESLRP	64 AAVGQAAHLS	456 LTSRVMIFSV	490 QCDFRANP
274 DKFLRHCESL	53 GPFAWPLIGN	454 KDLTSRVMIF	476 SKMQLFLF
264 LNRNFSNFIL	39 LLRQRRRLR	452 INKDLTSRVM	438 ENFDPARF
216 HDDPEFRELL	11 WPLNPLSIQQ	451 LINKDLTSRV	409 VLGYPHIPK
185 SADGAFLDPR	3 TSLSPNDPWP	448 KDGLINKDLT	386 YEAMRFSS
176 ELVALLVRGS	501 AKMNFSYGLT	443 ARFLDKDGLI	359 ELDQVVGR
157 TRQPRSRQVL	499 EPAKMNFSYG	411 GYHIPKDTV	351 DVQTRVQA
142 KVQRRRAHSM	487 LAHQCDFRAN	405 ANTSVLGYHI	346 FTRYPDVQ
134 FGHYSEHWKV	474 ELSKMQLFLF	400 PHATTANTSV	269 SNFILDKF
119 AFASFRRVSG	469 RCIGEELSKM	398 TIPHATTANT	261 FEQLNRNF

101 RAIHQALVQQ	459 RVMIFSVGKR	393 SFVPVTIPHA	255 RTVFREFE
76 RLARRYGDVF	443 ARFLDKDGLI	386 YEAMRFSSFV	254 VRTVFREF
39 LLRQRRRQLR	440 FDPARFLDKD	385 LYEAMRFSSF	239 SLVDVMPW
532 AVQNLQAKET	438 ENFDPARFLD	380 YVLAFLYEAM	223 ELLSHNEE
525 SMELLD SAVQ	384 FLYEAMRFSS	374 DQPNLPYVLA	211 GCRYSHDD
524 ESMELLD SAV	381 VLAFLYEAMR	372 MGDQPNLPYV	209 CFGCRYSH
474 ELSKMQLFLF	370 PCMGDQPNLP	363 VVGRDRLPCM	176 ELVALLVR
459 RVMIFSVGKR	352 VQTRVQAELO	347 TRYPDVQTRV	171 LSEARELV
443 ARFLDKDGLI	334 TLSTALQWLL	345 LFTRYPDVQT	157 TRQPRSRQ
442 PARFLDKDGL	309 HGGGARLDLE	337 TALQWLLLLF	154 NFFTRQPR
423 NQWSVNHDPL	295 AFILSAEKKA	329 GASQDTLSTA	142 KVQRRRAH
421 FVNQWSVNHD	262 EQLNRNFSNF	319 NVPATITDIF	141 WKVQRRRA
411 GYHIPKDTVV	252 NPVRTVFREF	295 AFILSAEKKA	127 SGGRSMAF
400 PHATTANTSV	246 WLQYFPNPVR	286 GAAPRDMMDA	75 ARLARRYG
394 FVPVTIPHAT	244 MPWLQYFPNP	283 LRPGAAPRDM	72 LSFARLAR
337 TALQWLLLLF	232 GRTVGAGSLV	267 NFSNFILDKF	36 QORLLRQR
318 ENVPATITDI	226 SHNEEFGRTV	262 EQLNRNFSNF	4 SLSPNDPW
313 ARLDLENVPA	188 GAFLDPRPLT	248 QYFPNPVRTV	504 NFSYGLTI
196 LTVVAVANVM	169 HVLSEARELV	247 LQYFPNPVRT	481 FLFISILA
188 GAFLDPRPLT	134 FGHYSEHWKV	201 VANVMSAVCF	477 KMQLFLFI
150 SMMRNFFTRQ	122 SFRVVS GGRS	199 VAVANVMSAV	466 GKRR CIGE
117 RPAFASFRVV	89 LGSCPIVVLN	198 VVAVANVMSA	457 TSRVMIFS
85 FQIRLGSCPI	76 RLARRYGDVF	195 PLTVVAVANV	407 TSVLG YHI
80 RYGDVFQIRL	73 SFARLARRYG	188 GAFLDPRPLT	399 IPHATTAN
60 IGNAAAVGQA	69 AAHLSFARLA	177 LVALLVRGSA	395 VPVTIPHA
28 SVLATVHVQG	68 QAAHLSFARL	165 VLEGHVLSA	381 VLAFLYEA
531 SAVQNLQAKE	58 PLIGNAAAVG	156 FTRQPRSRQV	366 RDRLPCM G
523 RESMELLD SA	29 VLATVHVQGQR	146 RAAHSMMRNF	349 YPDVQTRV
513 PKSFKVNVTL	22 TLLLLLSVLA	143 VORRAAHSMM	342 LLLL FTRY
508 GLTIKPKSFK	15 PLSIQQTTL	124 RVVSGGRSMA	341 WLLLLFTR
475 LSKMQLFLFI	8 NDPWPLNPLS	94 IVVLNGERAI	339 LQWLLLLF
473 EELSKMQLFL	527 ELLDSAVQNL	69 AAHLSFARLA	317 LENVPATI
462 IFSVGKRRCI	518 VNVTLRESME	66 VGQAAHLSFA	314 RLDLENVP
453 NKDLTSRVM I	512 KPKSFKVNV T	55 FAWPLIGNAA	297 ILSAEKKA
447 DKDGLINKDL	507 YGLTIKPKSF	22 TLLLLLSVLA	272 ILDKFLRH
426 SVNHDPLKWP	495 ANPNEPAKMN	20 QTTLLLLLSV	250 FPNPVRTV
405 ANT SVLG YHI	488 AHQCDFRANP	509 LTIKPKSFKV	246 WLQYFPNP
397 VTIPHATTAN	485 SILAHQCDFR	484 ISILAHQCDF	244 MPWLQYFP
389 MRFSSFPVPT	481 FLFISILAHQ	409 VLG YHIPKDT	243 VMPWLQYF
371 CMGDQPNLPY	476 SKMQLFLFIS	396 PVTIPHATTA	231 FGRTVGAG
368 RLPCM GDQPN	467 KRCIGEEELS	394 FVPVTIPHAT	195 PLTVVAVA
357 QAELOQVVGR	460 VMIFSVGKRR	343 LLLFTRYPDV	165 VLEGHVLS
346 FTRYPDVQTR	458 SRVMIFSVGK	316 DLENVPATIT	156 FTRQPRSR
328 FGASQDTLST	448 KDGLINKDLT	315 LDLENVPATI	143 VQRRRAHS
303 KAAGDSHGGG	446 LDKDGLINKD	311 GGARLDLENV	128 GGRSMAFG
268 FSNFILDKFL	426 SVNHDPLKWP	296 FILSAEKKAA	99 GERAHQA
246 WLQYFPNPVR	424 QWSVNHDPLK	279 HCESLRPGAA	92 CPIVVLNG
245 PWLQYFPNPV	422 VNQWSVNHD P	263 QLN RNFSNFI	87 IRLGSCPI

232 GRTVGAGSLV	421 FVNQWSVNHD	259 REFEQLNRNF	71 HLSFARLA
200 AVANVMSAVC	419 VVFNQWSVN	245 PWLQYFPNPV	67 GQAAHLSF
187 DGAFDPRPL	414 IPKDTVVFVN	225 LSHNEEFGR	29 VLATVHVG
161 RSRQVLEGHV	409 VLGYPKDT	222 RELLSHNEEF	26 LLSVLATV
98 NGERAIHQAL	405 ANTSVLGYHI	212 CRYSHDDPEF	24 LLLSVLA
83 DVFQIRLGSC	389 MRFSSFPVPT	196 LTVVAVANVM	22 TLLLLLSV
69 AAHLSFARLA	386 YEAMRFSFV	169 HVLSEARELV	531 SAVQNLQA
49 SAPPGPFAWP	380 YVLAFLYEAM	142 KVQRRAAHSM	528 LLDSAVQN
46 QLRSAAPPGF	374 DQPNLPYVLA	116 DRPAFASFRV	509 LTIKPKSF
41 RQRRRQLRSA	364 VGRDRLPCM	105 QALVQQGSAF	492 DFRANPNE
512 KPKSFKNVT	361 DQVVGRDRLP	104 HQALVQQGSA	485 SILAHQCD
483 FISILAHQCD	358 AELDQVGRD	97 LGERAIHQ	470 CIGEELSK
480 LFLFISILAH	356 VQAELDQVVG	85 FOIRLGSCPI	467 KRCIGEE
470 CIGEELSKMQ	344 LLFTRYPDVQ	54 PFAWPLIGNA	456 LSRVMIF
461 MIFSVGKRR	342 LLLFTRYPD	24 LLLSVLATV	441 DPARFLDK
460 VMIFSVGKRR	327 IFGASQDTLS	12 PLNPLSIQQT	436 NPENFDPA
446 LDKDGLINKD	313 ARLDLENVPA	507 YGLTIKPKSF	434 WPNPENFD
404 TANTSVLGYH	304 AAGDSHGGGA	479 QLFLFISILA	433 KWPNPENF
395 VPVTIPHATT	300 AEKKAAGDSH	472 GEELSKMQLF	430 DPLKWPNP
377 NLPYVLAFLY	294 DAFILSAEKK	431 PLKWPNPENF	388 AMRFSFV
358 AELDQVGRD	284 RPGAAPRDM	418 TVVFNQWSV	369 LPCMGDQP
339 LQWLLLLFTR	275 KFLRHCESLR	410 LGYHIPKDTV	368 RLPCMGDQ
322 ATITDIFGAS	267 NFSNFILDKF	382 LAFLYEAMRF	343 LLFTRYP
321 PATITDIFGA	261 FEQLNRNFSN	379 PYVLAFLYEA	334 TLSTALQW
298 LSAEKKAAGD	256 TVFREFEQLN	362 QVGRDRLPC	316 DLENVPAT
295 AFILSAEKKA	237 AGSLVDVMPW	354 TRVQAELDQV	290 RDMMDAFI
243 VMPWLQYFPN	229 EEFGRTVGAG	325 TDIFGASQDT	289 PRDMMDAF
223 ELLSHNEEF	208 VCFGCRYSHD	321 PATITDIFGA	284 RGAAPRD
204 VMSAVCFGCR	207 AVCFGCRYSH	297 ILSAEKKAAG	265 NRNFSNFI
181 LVRGSADGAF	206 SAVCFGCRY	241 VDVMPWLQYF	263 QLNRNFSN
120 FASFRVVSGG	202 ANVMSAVCFG	237 AGSLVDVMPW	253 PVRTVFRE
116 DRPAFASFRV	200 AVANVMSAVC	233 RTVGAGSLVD	252 NPVRTVFR
114 FADRPAFASF	198 VVAVANVMSA	232 GRTVGAGSLV	214 YSHDDPEF
95 VVLNGERAIH	197 TVVAVANVMS	226 SHNEEFGR	206 SAVCFGCR
93 PIVVLNGERA	195 PLTVVAVANV	180 LLVRGSADGA	203 NVMSAVCF
66 VGQAAHLSFA	193 PRPLTVVAVA	138 SEHWKVQRR	201 VANVMSAV
65 AVGQAAHLSF	183 RGSADGAFLD	134 FGHYSEHWKV	194 RPLTVVAV
64 AAVGQAAHLS	182 VRGSADGAFL	123 FRVVS GGSRM	188 GAFLDPRP
62 NAAAVGQAAH	179 ALLVRGSADG	119 AFASFRVVS	185 SADGAFLD

56 AWPLIGNAAA	178 VALLVRGSAD	115 ADRPAFASFR	183 RGSADGAF
510 TIKPKSFKVN	176 ELVALLVRGS	93 PIVVLNGERA	181 LVRGSADG
455 DLTSRVMIFS	163 RQVLEGHVLS	70 AHLSEFARLAR	180 LLVRGSAD
412 YHIPKDTVVF	158 RQPRSRQVLE	13 LNPLSIQQT	178 VALLVRGS
379 PYVLAFLYEA	155 FFTRQPRSRQ	439 NFDPARFLDK	161 RSRQVLEG
349 YPDVQTRVQA	148 AHSMMRNFFT	402 ATTANTSVLG	151 MMRNFFTR
283 LRPGAAPRDM	147 AAHSMMRNFF	229 EEFGRTVGAG	148 AHSMMRNF
278 RHCESLRPGA	143 VQRRAAHSMM	200 AVANVMSAVC	144 QRRAAHSM
247 LQYFPNPVRT	138 SEHWKVQRRR	186 ADGAFLDPRP	117 RPAFASFR
207 AVCFGCYRSH	131 SMAFGHYSEH	174 ARELVALLVR	116 DRPAFASF
201 VANVMSAVCF	127 SGGRSMAFGH	126 VSGGRSMAFG	115 ADRPAFAS
191 LDPRPLTVVA	125 VVSGGRSMAF	118 PAFASFRVVS	112 SAFADRPCA
178 VALLVRGSAD	124 RVVSGGRSMA	100 ERAIHQALVQ	107 LVQQGSAF
175 RELVALLVRG	123 FRVSGGRSM	89 LGSCPIVVLN	106 ALVQQGSA
151 MMRNFFTRQP	120 FASFRVVSGG	77 LARRYGDVFO	88 RLGSCPIV
125 VVSGGRSMAF	119 AFASFRVVSG	43 RRRQLRSAPP	80 RYGDVFOI
124 RVVSGGRSMA	118 PAFASFRVVS	521 TLRESMELLD	58 PLIGNAAA
104 HQALVQQGSA	112 SAFADRPCAFA	514 KSFKVNVTLR	57 WPLIGNAA
91 SCPIVVLNGE	106 ALVQQGSAFA	488 AHQCDFRANP	51 PPGPFAWP
90 GSCPIVVLNG	102 AIHQALVQQG	457 TSRVMIFSOG	50 APPGPFAW
89 LGSCPIVVLN	99 GERAIHQALV	415 PKDTVVVFVNQ	49 SAPPGPFA
77 LARRYGDVFO	95 VVLNGERAIH	403 TTANTSVLGY	48 RSAPPGPF
61 GNAAAVGQAA	91 SCPIVVLNGE	397 VTIPHATTAN	43 RRRQLRSA
51 PPGPFAWPLI	88 RLGSCPIVVL	391 FSSFVPVTIP	42 QRRRQLRS
34 HVGQRLLRQR	84 VFQIRLGSCP	371 CMGDQPNLPY	38 RLLRQRRR
33 VHVGRLLRQ	78 ARRYGDVFOI	356 VQAELDQVVG	25 LLSVLAT
13 LNPLSIQQT	74 FARLARRYGD	353 QTRVQAELDQ	15 PLSIQQT
529 LDSAVQNLQA	56 AWPLIGNAAA	327 IFGASQDTLS	14 NPLSIQQT
516 FKVNVTLRES	50 APPGPFAWPL	322 ATITDIFGAS	12 PLNPLSIQ
505 FSYGLTIKPK	38 RLLRQRRRQL	310 GGGARLDLEN	483 FISILAHQ
501 AKMNFSYGLT	35 VGQRLLRQRR	305 AGDSHGGGAR	413 HIPKDTVV
487 LAHQCDFRAN	28 SVLATVHVGO	303 KAAGDSHGGG	401 HATTANTS
476 SKMQLFLFIS	25 LLSVLATVH	282 SLRPGAAPRD	382 LAFLYEAM
464 SVGKRRRCIGE	533 VQNLQAKETC	280 CESLRPGAAP	357 QAELDQVV
454 KDLTSRVMIF	532 AVQNLQAKET	276 FLRHCESLRP	329 GASQDTLS
440 FDPARFLDKD	517 KVNVTLRESM	272 ILDKFLRHCE	296 FILSAEKK
437 PENFDPARFL	516 FKVNVTLRES	257 VFREFEQLNR	236 GAGSLVDV
434 WPNPENFDPA	513 PKSFKVNVTL	253 PVRTVFREFE	199 VAVANVMS
402 ATTANTSVLG	508 GLTIKPKSEK	213 RYSHDDPEFR	114 FADRPCAFA
382 LAFLYEAMRF	493 FRANPNEPAK	204 VMSAVCFGCR	105 QALVQQGS
375 QPNLPYVLAF	492 DFRANPNEPA	202 ANVMSAVCFG	93 PIVVLNGE
362 QVVGRDRLPC	486 ILAQCDFRAN	185 SADGAFLDPR	69 AAHLSEFAR
359 ELQVVGDRDR	483 FISILAHQCD	184 GSADGAFLDP	63 AAVGQAA
356 VQAELDQVVG	470 CIGEELSKMQ	183 RGSADGAFLD	55 FAWPLIGN
345 LFTRYPDVQT	466 GKRRRCIGEEL	136 HYSEHWKVQR	30 LATVHVGO

289 PRDMMDAFIL	465 VGKRRRCIGEE	113 AFADRPAFAS	524 ESMEL LDS
287 AAPRDMMDAF	462 IFSVGKRRCI	108 VQQGSAFADR	494 RANPNEPA
242 DVMPWLQYFP	454 KDLTSRVMIF	90 GSCPIVVLNG	487 LAHQCDFR
240 LVDVMPWLQY	452 INKDLTSRVM	79 RRYGDFVQIR	461 MIFSVGKR
236 GAGSLVDVMP	450 GLINKDLTSR	64 AAVGQAAHLS	451 LINKDLTS
233 RTVGAGSLVD	433 KWPNNPENFDP	62 NAAAVGQAAH	404 TANTSVLG
193 PRPLTVVAVA	431 PLKWPNNPENF	58 PLIGNAAAVG	398 TIPHATTA
159 QPRSRQVLEG	430 DPLKWPNNPEN	48 RSAPPGPFAW	326 DIFGASQD
147 AAHSMMRNFF	427 VNHDPLKWPNN	42 QRRRQLRSAP	323 TITDIFGA
132 MAFGHYSEHW	420 VVFVNQWSVNH	33 VHVQGRLLRQ	304 AAGDSHGG
123 FRVVS GGRSM	416 KDTVVVFVNQW	515 SFKVNVTLR	303 KAAGDSHG
107 LVQQGSAFAD	413 HIPKDTVVFV	510 TIKPKSFKVN	294 DAFILSAE
105 QALVQQGSAF	411 GYHIPKDTV	505 FSYGLTIKPK	287 AAPRDMMD
74 FARLARRYGD	401 HATTANTSVL	504 NFSYGLTIKP	226 SHNEEFGR
54 PFAWPLIGNA	400 PHATTANTSV	493 FRANPNEPAK	147 AAHSMMRN
53 GPFAPLIGN	395 VPVTIPHATT	480 LFLFISILAH	146 RAAHSMMR
47 LRSAPPGPFA	394 FVPVTIPHAT	468 RRCIGEELSK	132 MAFGHYSE
27 LSVLATVHVG	387 EAMRFS SFVP	467 KRCIGEELS	118 PAFASFRV
530 DSAVQNLQAK	383 AFLYEAMRFS	463 FSVGKRRCIG	102 AIHQALVQ
522 LRESMEL LDS	368 RLPCM GDQPN	459 RVMIFSVGKR	101 RAIHQALV
514 KSFKVNVTLR	363 VVGRDRLPCM	444 RFLDKDGLIN	68 QAAHLSFA
465 VGKRRRCIGEE	360 LDQVVGRDRL	428 NHDPLKWPNN	64 AAVGQAAH
452 INKDLTSRVM	355 RVQAELDQVV	424 QWSVNHDPK	62 NAAAVGQA
432 LKWPNNPENFD	350 PDVQTRVQAE	408 SVLGYHIPKD	59 LIGNAAAV
431 PLKWPNNPENF	348 RYPDVQTRVQ	387 EAMRFS SFVP	525 SMEL LDSA
419 VVFVNQWSVN	343 LLLFTRYPDV	383 AFLYEAMRFS	506 SYGLTIKP
414 IPKDTVVFVN	341 WLLLLFTRY	370 PCMGDQPNLP	471 IGEELSKM
396 PVTIPHATTA	326 DIFGASQDTL	366 RDRLPCM GDQ	356 VQAELDQV
324 ITDIFGASQD	323 TITDIFGASQ	358 AELDQVVGRD	227 HNEEFGR
312 GARLDLENVP	312 GARLDLENVP	357 QAELDQVVGR	167 EGHVLSEA
309 HGGGARLDLE	306 GDSHGGGARL	348 RYPDVQTRVQ	162 SRQVLEGH
294 DAFILSAEKK	303 KAAGDSHGGG	346 FTRYPDVQTR	136 HYSEHWKV
277 LRHCESLRPG	297 ILSAEKKAAG	331 SQDTLSTALQ	533 VQNLQAKE
267 NFSNFILDKF	296 FILSAEKKA	312 GARLDLENVP	484 ISILAHQC
266 RNFSNFILDK	288 APRDMMDAFI	309 HGGGARLDLE	472 GEELSKMQ
250 FPNPVRTVFR	287 AAPRDMMDAF	302 KKAAGDSHGG	462 IFSVGKRR
237 AGSLVDVMPW	285 PGAAPRDMMD	300 AEKKAAGDSH	458 SRVMIFS
225 LSHNEEFGR	283 LRPGAAPRDM	292 MMDAFILSAE	435 PNPENFDP
206 SAVCFGC RYS	280 CESLRPGAAP	290 RDMMDAFILS	426 SVNHDPLK
203 NVMSAVCFGC	278 RHCESLRPGA	281 ESLRPGAAPR	419 VVFVNQWS
202 ANVMSAVCFG	271 FILDKFLRHC	270 NFILDKFLRH	408 SVLGYHIP
197 TVVAV-ANVMS	264 LNRNFSNFIL	266 RNFSNFILDK	394 FVPVTIPH
174 ARELVALLVR	263 QLNRNFSNFI	260 EFEQLNRNFS	393 SFVPVTIP
148 AHSMMRNFFT	259 REFEQLNRNF	242 DVMPWLQYFP	331 SQDTLSTA

146 RAAHSMMRNF	254 VRTVREFEFQ	240 LVDVMPWLQY	318 ENVPATIT
138 SEHWKVQRRR	253 PVRTVREFEF	236 GAGSLVDVMP	315 LDLENVPA
113 AFADRPAPAS	251 PNPVRTVFRE	230 EFGRTVGAGS	281 ESLRPGAA
81 YGDVFQIRLG	243 VMPWLQYFNP	227 HNEEFGRTVG	278 RHCESLRP
70 AHLSEFARLAR	241 VDVMPWLQYF	220 EFRELLSHNE	260 EFEQLNRN
507 YGLTIKPKSF	236 GAGSLVDVMP	211 GCRYSHDDPE	259 REFEQLNR
506 SYGLTIKPKS	231 FGRTVGAGSL	207 AVCFGCRYSH	238 GSLVDVMP
503 MNFSYGLTIK	230 EFGRTVGAGS	197 TVVAVANVMS	232 GRTVGAGS
493 FRANPNPEAK	224 LLSHNEEFGR	179 ALLVRGSADG	230 EFGRTVGA
482 LFISILAHQC	223 ELLSHNEEFG	176 ELVALLVRGS	221 FRELLSHN
458 SRVMIFSVGK	222 RELLSHNEEF	175 RELVALLVRG	215 SHDDPEFR
448 KDGLINKDLT	210 FGCRYSHDDP	164 QVLEGHVLS	198 VVAVANVM
416 KDTVFEVNQW	201 VANVMSAVCF	163 RQVLEGHVLS	172 SEARELVA
406 NTSVLGYHIP	199 VAVANVMSAV	158 RQPRSRQVLE	168 GHVLSEAR
399 IPHATTANTS	191 LDPRPLTVVA	151 MMRNFFTRQP	150 SMMRNFFT
374 DQPNLPYVLA	186 ADGAFLDPRP	150 SMMRNFFTRQ	139 EHWKVQRR
353 QTRVQAELDQ	181 LVRGSADGAF	145 RRAAHSMMRN	134 FGHYSEHW
325 TDIFGASQDT	180 LLVRGSADGA	144 QRRAAHSMMR	131 SMAFGHYS
317 LENVPATITD	177 LVALLVRGSA	140 HWKVQRRRAH	123 FRVVSGGR
302 KKAAGDSHGG	152 MRNFFTRQPR	133 AFGHYSEHWK	104 HQALVQQG
299 SAEKKAAGDS	144 QRRAAHSMMR	130 RSMAFGHYSE	94 IVVLNGER
293 MDAFILSAEK	140 HWKVQRRRAH	128 GGRSMAFGHY	91 SCPIVVLN
256 TVFREFEQLN	139 EHWKVQRRRA	120 FASFRVVSGG	73 SFARLARR
241 VDVMPWLQYF	135 GHYSEHWKVQ	102 AIHQALVQQG	28 SVLATVHV
229 EEFGRTVGAG	133 AFGHYSEHWK	101 RAIHQALVQQ	2 GTSLSPND
228 NEEFGRTVGA	132 MAFGHYSEHW	82 GDVFQIRLGS	530 DSAVQNLQ
194 RPLTVVAVAN	129 GRSMAGHY	74 FARLARRYGD	526 MELLDSAV
184 GSADGAFLDP	113 AFADRPAPAS	71 HLSFARLARR	520 VTLRESME
143 VQRRAAHSMM	105 QALVQQGSFA	67 GQAAHLSFAR	518 VNVTLRES
137 YSEHWKVQRR	93 PIVVLNGERA	59 LIGNAAVVGQ	517 KVNVTLRE
126 VSGGRSMAFG	92 CPIVVLNGER	49 SAPPGPFAWP	516 FKVNVTLR
108 VQQGSFAADR	85 FQIRLGSCPI	44 RRQLRSAPP	511 IKPKSFKV
48 RSAPPGPFAW	75 ARLARRYGDV	39 LLRQRRRQLR	505 FSYGLTIK
32 TVHVGQRLLR	71 HLSFARLARR	32 TVHVGQRLLR	493 FRANPNPE
6 SPNDPWPLNP	66 VGQAAHLSFA	28 SVLATVHVQ	489 HQCDFRAN
2 GTSLSPNDPW	63 AAAGVQAAHL	2 GTSLSPNDPW	460 VMIFSVGK
533 VQNLQAKETC	61 GNAAAVGQAA	530 DSAVQNLQAK	453 NKDLTSRV
526 MELLDSAVQN	60 IGNAAAVGQA	526 MELLDSAVQN	448 KDGLINKD

491 CDFRANPNP	47 LRSAPPGPFA	525 SMELLD SAVQ	443 ARFLDKDG
488 AHQCDFRANP	46 QLSAPPGPF	522 LRESMELLD	427 VNHDPLKW
484 ISILAHQCDF	42 QRRRQLRSAP	506 SYGLTIKPKS	424 QWSVNHDP
449 DGLINKDLTS	37 QRLLRQRRRQ	497 PNEPAKMNFS	422 VNQWSVNH
444 RFLDKDGLIN	30 LATVHVQGRL	495 ANPNEPAKMN	421 FVNQWSVN
430 DPLKWPNNPEN	26 LLSVLATVHV	490 QCDFRANPNE	420 VFNQWSV
391 FSSFVPVTIP	24 LLLLSVLATV	487 LAHQCDFRAN	417 DTVVFNQ
378 LPYVLAFLYE		485 SILAHQCDFR	416 KDTVVFVN
331 SQDTLSTALQ	HLA-A26 Nonamers	483 FISILAHQCD	411 GYHIPKDT
319 NVPATITDIF		464 SVGKRCIGE	406 NTSVLGYH
310 GGGARLDLEN	Pos 123456789	458 SRVMIFSVGK	397 VTIPHATT
284 RPGAAPRDM	242 DVMPWLQYF	449 DGLINKDLTS	391 FSSFVPVT
279 HCESLRPGAA	455 DLTSRVMIF	445 FLDKDG LINK	383 AFLYEAMR
258 FREFEQLNRN	470 CIGEELSKM	438 ENFDPARFLD	379 PYVLAFLY
257 VFREFEQLNR	223 ELLSHNEEF	435 PNPENFDPAR	373 GDQPNLPY
222 RELLSHNEEF	260 EFEQLNRNF	432 LKWPNNPENFD	365 GRDRLP CM
218 DPEFRELLSH	256 TVFREFEQL	425 WSVNHDP LKW	363 VVGRDRLP
212 CRYSHDDPEF	253 PVRTVFREF	420 VFNQWSVNH	361 DQVVGRDR
208 VCFGCRYSHD	528 LLDSAVQNL	416 KDTVVFVNQW	360 LDQVVGRD
136 HYSEHWKVQR	341 WLLLLFTRY	406 NTSVLGYHIP	352 VQTRVQAE
130 RSMAFGHYSE	263 QLNRFNSNF	392 SSFVPVTIPH	340 QWLLLLFT
121 ASFRVVS GGR	521 TLRESMELL	381 VLAFLYEAMR	327 IFGASQDT
118 PAFASFRVVS	479 QLFLFISIL	368 RLPCM GDQPN	324 ITDIFGAS
115 ADRPAFASFR	474 ELSKMQLFL	364 VGRDRLP CMG	311 GGARLDLE
111 GSAFADRP AF	473 EELSKMQLF	359 ELDQVVGRDR	309 HGGARLD
110 QGS AFADRP A	413 HIPKDTVVF	350 PDVQTRVQAE	306 GD SHGGA
92 CPIVVLNGR	381 VLAFLYEAM	342 LLLLLFTRYPD	295 AFILSAEK
73 SFARLARRYG	338 ALQWLLLLF	340 QWLLLLFTRY	279 HCESLRPG
67 GQA AHS FAR	377 NLPYVLAFL	332 QDTLSTALQW	268 FSNFILDK
45 RQLRSAPPGP	351 DVQTRVQAE	324 ITDIFGASQD	258 FREFEQLN
19 QQT TLLLLLS	239 SLVDVMPWL	307 DSHGGGARLD	241 VD VMPWLQ
496 NPNEPAKMNF	173 EARELVALL	301 EKKAAGDSHG	237 AGSLVDVM
492 DFRANPNEPA	106 ALVQQGSAF	298 LSAEKKAAGD	235 VGAGSLVD
468 RRCIGEELSK	22 TLLLLLSVL	293 MDAFILSAEK	222 RELLSHNE
463 FSVGKRRICIG	417 DTVVFNQW	285 PGAAPRDMMD	216 HDDPEFRE
439 NFDPARFLDK	359 ELDQVVGRD	246 WLQYFPNPVR	210 FGCRYSHD
428 NHDPLKWPNP	334 TLSTALQWL	224 LLSHNEEFGR	208 VCFGCRY S
425 WSVNHDP LKW	326 DIFGASQDT	223 ELLSHNEEFG	205 MSAVCFGC
420 VFNQWSVNH	220 EFRELLSHN	217 DDPEFRELLS	204 VMSAVCFG
417 DTVVFNQWS	176 ELVALLVRG	208 VCFGCRYSHD	196 LTVVAVAN
392 SSFVPVTIPH	520 VTLRESMEL	167 EGHVLSEARE	193 PRPLTVVA
385 LYEAMRFSS F	508 GLTIKPKSF	166 LEGHVLSEAR	182 VRGSADGA
383 AFLYEAMRFS	485 SILAHQCDF	160 PRSRQVLEGH	177 LVALLVRG
367 DR LPCM GDQP	336 STALQWLLL	153 RNFFTRQPRS	175 RELVALLV
320 VPATITDIFG	169 HVLSEAREL	152 MRNFFTRQPR	169 HVLSEARE
305 AGDSHGGGAR	124 RVVSGGRSM	149 HSM MRNFFTR	163 RQVLEGHV
300 AEKKAAGDSH	83 DVFQIRLGS	132 MAFGHYSEHW	155 FFTRQPRS
280 CESLRPGAAP	31 ATVHVQGRL	129 GRSMAGHYS	135 GHYSEHWK
275 KFLRHCESLR	499 EPAKMNF SY	122 SFRVVS GGRS	129 GRSMAGH

270 NFILDKFLRH
269 SNFILDKFLR
261 FEQLNRNFSN
259 REFEQLNRNF
221 FRELLSHNEE
214 YSHDDPEFRE
186 ADGAFLDPRP
166 LEGHVLSEAR
154 NFFTRQPRSR

149 HSMMRNFFTR
139 EHWKVQRRAA
133 AFGHYSEHWK
127 SGGRSMAFGH
103 IHQALVQQGS

79 RRYGDVFQIR
72 LSFARLARRY
40 LRQRRRQLRS
5 LSPNDPWPLN
3 TSLSPNDPWP
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515 SFKVNVTLCR
498 NEPAKMNFYSY
489 HQCDFRANPN
427 VNHDPLKWP
422 VNQWSVNHD
387 EAMRFSSFP
365 GRDR LPCMGD
364 VGRDR LPCMG
350 PDVQTRVQAE

340 QWLLLLFTRY

327 IFGASQDTLS
273 LDKFLRHCE
254 VRTVFREFEQ
252 NPVRTVFREF
249 YFPNPVRTVF
244 MPWLQYFPNP
219 PEFRELLSHN
217 DDPEFRELLS
205 MSAVCFGCRY

163 RQVLEGHVLS
160 PRSRQVLEGH
158 RQPRSRQVLE
145 RRAAHSMMRN

141 WKVQRRRAHS

140 HWKVQRRRAH
129 GRSMAGHYS

122 SFRVVS GGRS

82 GDVFQIRLGS

402 ATTANTSVL
73 SFARLARRY
17 SIQQTTL
527 ELLDSAVQN
383 AFLYEAMRF
333 DTLSTALQW
307 DSHGGGARL
197 TVVAVANVM
115 ADPAFASF

39 LLRQRRRQL
32 TVHVGQRLL
438 ENFDPARFL
394 FVPVTIPHA
386 YEAMRFSSF

376 PNLPHYVLA
322 ATITDIFGA
271 FILDKFLRH
230 EFGRTVGAG
217 DDPEFRELL
200 AVANVMSAV
177 LVALLVRGS
102 AIHQALVQQ
15 PLSIQQTTL
481 FLFISILAH
475 LSKMQLFLF
451 LINKDLTSR
404 TANTSVLGY
374 DQPNLPYVL
323 TITDIFGAS

288 APRDMMDAF

216 HDDPEFREL
196 LTVVAVANV
147 AAHSMMRNF
34 HVGQRLLRQ
21 TLLLLLLSV
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510 TIKPKSFKV
482 LFISILAHQ
447 DKDGLINKD

380 YVLAFLYEA
361 DQVVGRDRL
355 RVQAELDQV
344 LLFTRYPDV

327 IFGASQDTL

319 NVPATITDI
316 DLENVPATI

275 KFLRHCESL

272 ILDKFLRHC

121 ASFRVVS GGR
103 IHQALVQQGS
96 VLNGERAIHQ
95 VVLNGERAIH
73 SFARLARRYG
52 PGPFAPWPLIG
45 RQLRSAPPGP
40 LRQRRRQLRS
36 GQRLLRQRRR

29 VLATVHV GQR
27 LSVLATVHVG
25 LLLSVLATVH
19 QQTTL LLLLS
534 QNLQAKETCQ

531 SAVQNLQAKE
528 LLDSAVQNLQ
508 GLTIKPKSFK
503 MNFSYGLTIK
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489 HQCDFRANPN
481 FLFISILAHQ
476 SKMQLFLFIS
470 CIGEELSKMQ
455 DLTSRVMIFS
450 GLINKDLTSR
440 FDPARFLDKD
433 KWPNPENFDP
429 HDPLKWPNE
427 VNHDPLKWP

421 FVNQWSVNHD

419 VVFNQWSVN
407 TSVLGYHIPK
384 FLYEAMRFSS
367 DR LPCMGDQP
365 GRDR LPCMGD
344 LLFTRYPDVQ
341 WLLLLFTRY
323 TITDIFGASQ
317 LENVPATITD

299 SAEKKAAGDS
277 LRHCESLRPG
275 KFLRHCESLR
265 NRNFSNFILD

251 PNPVRTVFRE

243 VMPWLQYFPN
209 CFGCRYSHDD

205 MSAVCFGCRY

203 NVMSAVCFGC

125 VVSGGRSM
111 GSAFADRP
108 VQQGSAFA
103 IHQALVQQ
95 VVLNGERA
85 FQIRLGSC
81 YGDVFQIR
66 VGQAAHLS
61 GNAAAVGQ

60 IGNAAAVG
56 AWPLIGNA
35 VGQRLLRQ
27 LSVLATVH
21 TLLLLLS

13 LNPLSIQQ
10 PWPLNPLS

HLA-B8 Nonamers

Pos 123456789
39 LLRQRRRQL
173 EARELVALL
521 TLRESMELL
510 TIKPKSFKV
508 GLTIKPKSF
455 DLTSRVMIF
159 QPRSRQVLE
465 VGKRCRIGE
414 IPKDTVVVFV

288 APRDMMDAF

479 QLFLFISIL
474 ELSKMQLFL
473 EELSKMQLF
431 PLKWPNPEN
239 SLVDVMPWL
99 GERAIHQAL
528 LLDSAVQNL
512 KPKSFKVNV
467 KRCRIGEEL

463 FSVGKRRCI
450 GLINKDLTS
377 NLPYVLAFL
86 QIRLGSCPI

22 TLLLLLSVL

535 NLQAKETCQ
475 LSKMQLFLF

444 RFLDKDGLI

334 TLSTALQWL

43 RRRQLRSAPP 37 QRLLRQRRRQ	268 FSNFILDKF 203 NVMSAVCFG	178 VALLVRGSAD 155 FFTRQPRSRQ	299 SAEKKAAGD 223 ELLSHNEEF
11 WPLNPLSIQQ	172 SEARELVAL	141 WKVQRRRAHS	188 GAFLDPRPL
518 VNVTLRESME	165 VLEGHVLSE	137 YSEHWKVQRR	179 ALLVRGSAD
504 NFSYGLTIKP 495 ANPNEPAKMN	129 GRSMAGHY 69 AAHLSEFARL	135 GHYSEHWKVQ 131 SMAFGHYSEH	126 VSGGRSMAF 77 LARRYGDVF
467 KRRCIGEELS	20 QTTLTLLLS	127 SGGRSMAFGH	51 PPGPFAWPL
436 NPENFDPARF	524 ESMELDSA	109 QQGSADFADRP	17 SIQQTLLL
435 PNPENFDPAR 433 KWPENFDP 429 HDPLKWPNE 424 QWSVNHDPLK 370 PCMGDQPNLP 348 RYPDVQTRVQ 307 DSHGGGARLD 290 RDMMDAFILS 281 ESLRPGAAPR 253 PVRTVFREFE	509 LTIKPKSFK 497 PNEPAKMNF 461 MIFSVGKRR 456 LTRVMIFS 409 VLGYHIPKD 397 VTIPHATTA 384 FLYEAMRFS 364 VGRDRLPCM 236 GAGSLVDVM 181 LVRGSADGA	107 LVQQGSADFAD 81 YGDVFQIRLG 72 LSFARLARRY 37 QRLLRQRRRQ 35 VQQRLLRQRR 34 HVGQRLLRQR 8 NDPWPLNPLS 5 LSPNDPWPLN 3 TSLSPNDPWP	15 PLSIQQTTL 364 VGRDRLPCM 271 FILDKFLRH 190 FLDPRPLTV 120 FASFRVVS 69 AAHLSEFARL 515 SFKVNVTLR 500 PAKMNFSG 386 YEAMRFSS 344 LLFTYRDPV
251 PNPVRTVFRE 227 HNEEFGRFVG 210 FGCYSHDDP 209 CFGCRYSHDD 153 RNFFTRQPRS 135 GHYSEHWKVQ 128 GGRSMAFGHY 84 VFQIRLGSCP 44 RRQLRSAPPG 42 QRRRQLRSAP 36 GQRLLRQRRR 35 VQQRLLRQRR 10 PWPPLNPLSIQ 8 NDPWPLNPLS 499 EPAKMNFSG 497 PNEPAKMNF 438 ENFDPARFLD 415 PKDTVVFVNQ 361 DQVVGRDRLP 285 PGAAPRDMMD 262 EQLNRNFSNF 167 EGHVLEARE 260 EFEQLNRNFS 52 PGPFAPWPLIG 301 EKKAAGDSHG	126 VSGGRSMAF 125 VVSGGRSMA 112 SAFADPAF 58 PLIGNAAAV 28 SVLATVHVG 25 LLLSVLATV 24 LLLSVLAT 532 AVQNLQAKE 492 DFRANPNP 432 LKWPENP 421 FVNQWSVN 419 VVFVNQWSV 337 TALQWLLL 324 ITDIFGASQ 233 RTVGAGSLV 198 VVAVANVMS 164 QVLEGHVLS 156 FTRQPRSRQ 89 LGSCPIVVL 76 RLARRYGDV 64 AAVGQAAHL 19 QQTTLTLL 8 NDPWPLNPL 519 NVTRESME 514 KSFKVNVT 483 FISILAHQC	HLA-B*1510 Nonamers Pos 123456789 148 AHSMMRNFF 89 LGSCPIVVL 139 EHWKVQRR 438 ENFDPARFL 412 YHIPKDTVV 361 DQVVGRDRL 216 HDDPEFREL 32 TVHVGQRLL 514 KSFKVNVT 308 SHGGGARLD 307 DSHGGGARL 215 SHDDPEFRE 188 GAFLDPRPL 172 SEARELVAL 81 YGDVFQIRL 39 LLRQRRRQL 521 TLRESMELL 488 AHQCDFRAN 474 ELSKMQLFL 472 GEELSKMQL 428 NHDPLKWP 424 QWSVNHDPL 402 ATTANTSVL	337 TALQWLLL 282 SLRPGAAPR 218 DPEFRELLS 172 SEARELVAL 76 RLARRYGDV 64 AAVGQAAHL 41 RRRRQLRS 448 KDGLINKDL 336 STALQWLLL 331 SQDTLSTAL 320 VPATITDIF 298 LSAEKKAAG 286 GAAPRDMMD 276 FLRHCESLR 269 SNFILDKFL 253 PVRTVFREF 250 FPNPVRTVF 192 DPRPLTVVA 140 HWKVQRRRA 138 SEHWKVQRR 112 SAFADPAF 106 ALVQQGSFA 520 VTLRESMEL 514 KSFKVNVT 485 SILAHQCDF 472 GEELSKMQL
HLA-A*0201 Octamers Pos 12345678 531 SAVQNLQA 525 SMELDSA 494 RANPNEPA	459 RVMIFSVGK 441 DPARFLDKD 437 PENFDPARF 408 SVLGYHIPK 406 NTSVLGYHI 403 TTANTSVLG	374 DQPNLPYVL 327 IFGASQDTL 278 RHCESLRPG 239 SLVDVMPWL 232 GRTVGAGSL 226 SHNEEFGR	438 ENFDPARFL 429 HDPLKWPNP 413 HIPKDTVV 352 VQTRVQAE 338 ALQWLLLF 316 DLENVPATI

488 AHQCD FRA
481 FLFISILA
436 NPENFDPA
398 TIPHATTA
395 VPVTIPHA
381 VLAFLYEA
376 PNLPLYVLA
351 DVQTRVQA
331 SQDTLSTA
323 TITDIFGA
315 LDLENVPA
306 GDSHGGGA
298 LSAEKKAA
297 ILSAEKKA
293 MDAFILSA
288 APRDMMDA
281 ESLRPGAA
280 CESLRPGA
230 EFGRTVGA
200 AVANVMSA
195 PLTVVAVA
193 PRPLTVVA
182 VRGSADGA
179 ALLVRGSA
172 SEARELVA
167 EGHVLSEA
141 WKVQRRRA
140 HWKVQRRRA
126 VSGGRSMA
114 FADRPAFA
112 SAFADRP
108 VQQGSAFA
106 ALVQQGSA
99 GERAIHQ
95 VVLNGERA
71 HLSFARLA
68 QAAHLSFA
63 AAAGVQAA
62 NAAAGVQA
58 PLIGNAAA
57 WPLIGNAA
56 AWPLIGNA
49 SAPPGPFA
43 RRRQLRSA
24 LLLLSVLA

398 TIPHATTAN
390 RFSSFPVPT
372 MGDQPNLPY
370 PCMGDQPNL
367 DRLPCM GDQ
362 QVVGRDRLP
346 FTRYPDVQT
296 FILSAEKKA
250 FPNPVRTVF
229 EEFGRTVGA
213 RYSHDDPEF
209 CFGCRYSHD
202 ANVMSAVCF
182 VRGSADGAF
142 KVQRRAAHS
107 LVQQGSAFA
93 PIVVLNGER
54 PFAWPLIGN
18 IQQTTL LLL
16 LSIQQTTL L
12 PLNPLSIQ Q
515 SFKVNVTLR
495 ANPNEPAKM
472 GEELSKMQL
464 SVGKRRRCIG
450 GLINKDLTS
443 ARFLDKDGL
431 PLKWPNPEN
426 SVNHDPLKW
418 TVVFNQWS
396 PVTIPHATT
378 LPYVLAFLY
353 QTRVQAELD
331 SQDTLSTAL
320 VPATITDIF
294 DAFILSAEK
291 DMMDAFILS
282 SLRPGAAPR
269 SNFILDKFL
255 RTVFREFEQ
249 YFPNPVRTV
241 VDVMPWLQY
240 LVDVMPWLQ
206 SAVCFGCRY
190 FLDPRPLTV
158 RQPRSRQVL

173 EARELVALL
169 HVLSEAREL
168 GHVLSEARE
158 RQPRSRQVL
103 IHQALVQQG
22 TLLLLLSVL
400 PHATTANTS
370 PCMGDQPNL
337 TALQWLLLL
334 TLSTALQWL
309 HGGGARLDL
217 DDPEFRELL
163 RQVLEGHVL
99 GERAIHQAL
70 AHL SFARLA
69 AAHLSFARL
51 PPGPFAWPL
33 VHVGRQLLR
31 ATVHVGRQL
18 IQQTTL LLL
15 PLSIQQTTL
528 LLDSAVQNL
520 VTLRESMEL
479 QLFLFISIL
467 KRRCIGEEL
443 ARFLDKDGL
413 HIPKDTVVF
352 VQTRVQAEL
336 STALQWLLL
331 SQDTLSTAL
260 EFEQLNRNF
256 TVFREFEQL
250 FPNPVRTVF
183 RGSADGAFL
135 GHYSEHWKV
64 AAVGQAAHL
17 SIQQTTL LLL
16 LSIQQTTL L
8 NDPWPLNPL
5 LSPNDPWPL
501 AKMNFSYGL
497 PNEPAKMNF
462 IFSVGKRRRC
453 NKDLTSRVM
448 KDGLINKDL
432 LKWPNPENF

312 GARLDLENV
301 EKKAAGDSH
264 LNRNFSNFI
263 QLNRNFSNF
232 GRTVGAGSL
217 DDPEFRELL
216 HDDPEFRELL
169 HVLSEAREL
115 ADPAFAFAS
89 LGSCPIVVL
74 FARLARRYG
46 QLSAPP GP
513 PKSFKNVT
452 INKDLTSRV
443 ARFLDKDGL
442 PARFLDKDG
424 QWSVNHDPL
361 DQVGRDRL
327 IFGASQDTL
309 HGGGARLDL
265 NRNFSNFIL
262 EQLNRNFSN
229 EEFGRTVGA
163 RQVLEGHVL
81 YGDVFQIRL
32 TVHVGRQLL
18 IQQTTL LLL
501 AKMNFSYGL
498 NEPAKMNFS
464 SVGKRRRCIG
446 LDKDGLINK
412 YHIPKDTVV
402 ATTANTSVL
374 DQPNLPYVL
370 PCMGDQPNL
351 DVQTRVQA
335 LSTALQWLL
307 DSHGGGARL
300 AEKKAAGDS
290 RDMMDAFIL
280 CESLRPGAA
275 KFLRHCESL
274 DKFLRHCE
273 LDKFLRHCE
256 TVFREFEQL
251 PNPVRTVFR

HLA-A*0202 Nonamers

Pos 123456789
535 NLQAKETCQ
529 LDSAVQNLQ
498 NEPAKMNFS
492 DFRANPNEP
485 SILAHQCDF
440 FDPARFLDK
402 ATTANTSVL
399 IPHATTANT
385 LYEAMRFSS

96 VLNGERAIH
95 VVLNGERAI
94 IVVLNGERA
84 VFQIRLGSC
66 VGQAAHLSF
65 AVGQAAHLS
59 LIGNAAAVG
46 QLSAPP GP
29 VLATVHVGG
4 SLSPNDPW
2 GTSLSPNDP
518 VNVTLRESM

377 NLPYVLAFL
376 PNLPLYVLAFL
335 LSTALQWLL
290 RDMMDAFIL
275 KFLRHCESL
269 SNFILDKFL
265 NRNFSNFIL
236 GAGSLVDVM
19 QQTTL LLL
437 PENFDPAF
288 APRDMMDAF
285 PGAAPRDMM

220 EFRELLSHN
183 RGSADGAFL
158 RQPRSRQVL
149 HSMNRNFFT
147 AAHSMNRNF
97 LNGERAIHQ
31 ATVHVGRQL
19 QQTTL LLL
16 LSIQQTTL L
8 NDPWPLNPL
5 LSPNDPWPL
527 ELLDSAVQN

380 YVLAFLYEA	504 NFSYGLTIK	284 RPGAAPRDM	519 NVTLRESME
355 RVQAELDQV	486 ILAHQCDFR	253 PVRTVFREF	499 EPAKMNFSY
335 LSTALQWLL	445 FLDKDGLIN	213 RYSHDDPEF	496 NPNEPAKMN
327 IFGASQDTL	368 RLPCMGRDQP	197 TVVAVANVM	481 FLFISILAH
319 NVPATITDI	363 VVGRDRLPC	147 AAHSMMRNF	466 GKRRCIGEE
310 GGGARLDLE	352 VQTRVQAE	124 RVVSGGRSM	440 FDPARFLDK
302 KKAAGDSHG	314 RLDLENVPA	112 SAFADRPAP	409 VLGYPHIPKD
301 EKKAAGDSH	309 HGGGARLDL	47 LRSAPPGPF	384 FLYEAMRFS
297 ILSAEKKAA	295 AFILSAEKK	508 GLTIKPKSF	359 ELQVVGGRD
292 MMDAFILSA	285 PGAAPRDM	473 EELSKMQLF	346 FTRYPDVQT
285 PGAAPRDM	267 NFSNFILDK	386 YEAMRFSSS	314 RLDLENVPA
284 RPGAAPRDM	259 REFEQLNRN	383 AFLYEAMRF	310 GGGARLDLE
234 TVGAGSLVD	234 TVGAGSLVD	381 VLAFLYEAM	297 ILSAEKKAA
204 VMSAVCFGC	207 AVCFGC RYS	364 VGRDRLPCM	260 EFEQLNRNF
199 VAVANVMSA	195 PLTVVAVAN	248 QYFPNPVRT	257 VFREFEQLN
197 TVVAVANVM	192 DPRPLTVVA	242 DVMPWLQYF	255 RTVFREFEQ
186 ADGAFLDPR	188 GAFLDPRPL	223 ELLSHNEEF	195 PLTVVAVAN
183 RGSADGAFL	187 DGAFLDPRP	202 ANVMSAVCF	176 ELVALLVRG
176 ELVALLVRG	179 ALLVRGSAD	126 VSGGRSMAF	170 VLSEARELV
171 LSEARELVA	170 VLSEARELV	115 ADRPAPASF	141 WKVQRRRAH
145 RRAAHSMMR	154 NFFTRQPRS	106 ALVQQGSAF	122 SFRVVS GGR
144 QRRAAHSMM	148 AHSMMRNF	77 LARRYGDVF	84 VFQIRLGSC
130 RSMAGHYHS	144 QRRAAHSMM	518 VNVTLRESM	44 RRQLRSAPP
118 PAFASFRVV	132 MAGHYSEH	495 ANPNEPAKM	37 QRLLRQRRR
116 DRPAFASFR	99 GERAIHQAL	470 CIGEELSKM	34 HVGQRLLRQ
112 SAFADRPAP	86 QIRLGSCPI	455 DLTSRVMIF	24 LLLSVLAT
110 QGSFAADRP	81 YGDVFQIRL	320 VPATITDIF	490 QCDFRANPN
103 IHQALVQQG	77 LARRYGDVF	263 QLNRNFSNF	476 SKMQLFLFI
99 GERAIHQAL	51 PPGPFAWPL	182 VRGSADGAF	457 TSVRMIFSV
75 ARLARRYGD	47 LRSAPPGPF	485 SILAHQCDF	395 VPVTIPHAT
72 LSFARLARR	38 RLLRQRRRQ	475 LSKMQLFLF	391 FSSFVPVTI
67 GQAAHLSFA	23 LLLLSVLA	414 IPKDTVVFV	381 VLAFLYEAM
66 VGQAAHLSF	9 DPWPLNPLS	349 YPDVQTRVQ	376 PNLPYVLA
62 NAAAVGQAA	535 NLQAKETCQ	338 ALQWLLLLF	375 QPNLPYVLA
61 GNAAAVGQA	530 DSAVQNLQA	268 FSNFILDKF	362 QVVGDRDRLP
60 IGNAAAVGQ	501 AKMNFSYGL	249 YFPNPVRTV	211 GCRYSHDDP
53 GPFAPWPLIG	467 KRRCIGEEI	192 DPRPLTVVA	209 CFGCRYSHD
47 LRSAPPGPF	453 NKDLTSRVM	144 QRRAAHSMM	182 VRGSADGAF
28 SVLATVHVG	439 NFDPARFLD	143 VQRRAAHSM	171 LSEARELVA
	389 MRFSSFVPV	119 AFASFRVVS	165 VLEGHVLSE
HLA-A*0202 Decamers			
Pos 1234567890	335 LSTALQWLL	90 GSCPIVVLN	157 TRQPRSRQV
	297 ILSAEKKAA	66 VGQAAHLSF	154 NFFTRQPRS
	276 FLRHCESLR	511 IKPKSFKVN	142 KVQRRAAHS
63 AA AVGQAAHL	274 DKFLRHCE	494 RANPNEPAK	113 AFADRPAPA
303 KAAGDSHGGG	265 NRNFSNFIL	452 INKDLTSRV	95 VVLNGERAI
286 GAAPRDMMDA	257 VFREFEQLN	391 FSSFVPVTI	78 ARRYGDVFQ
146 RAAHSMMRNF	235 VGAGSLVDV	390 RFSSFVPVT	75 ARLARRYGD
68 QAAHLSFARL	232 GRTVGAGSL	373 GDQPNLPYV	72 LSFARLARR
62 NAAAVGQAAH	183 RGSADGAFL	359 ELQVVGGRD	71 HLSFARLAR
200 AVANVMSAVC	180 LLVRGSADG	357 QAELDQVVG	57 WPLIGNAAA
119 AFASFRVVSG	143 VQRRAAHSM	347 TRYPDVQTR	40 LRQRRRQLR
113 AFADRPAPAS	119 AFASFRVVS	315 LDLENVPAT	36 GQRLLRQRR
530 DSAVQNLQAK	113 AFADRPAPA	297 ILSAEKKAA	29 VLATVHVGO
499 EPAKMNFSY	88 RLGSCPIVV	272 ILDKFLRHC	23 LLLLSVLA
493 FRANPNEPAK	71 HLSFARLAR	228 NEEFGRTVG	6 SPNDPWPLN

486 ILAHQCDFRA	26 LLSVLATVH	227 HNEEFGRV	4 SLSPNDPWP
441 DPARFLDKDG	5 LSPNDPWPL	176 ELVALLVRG	531 SAVQNLQAK
403 TTANTSVLGY	460 VMIFSVGKR	157 TRQPRSRQV	492 DFRANPNEP
400 PHATTANTSV	448 KDGLINKDL	156 FTRQPRSRQ	486 ILAHQCDFR
386 YEAMRFSSFV	444 RFLDKDGLI	140 HWKVQRRRA	454 KDLTSRVM
381 VLAFLYEAMR	424 QWSVNHDPL	137 YSEHWKVQR	445 FLDKDGLIN
356 VQAELDQVVG	420 VVFNQWSVN	94 IVVLNGERA	436 NPENFDPAR
336 STALQWLLLL	393 SFVPVTIPH	73 SFARLARRY	434 WPNPENFDP
328 FGASQDTLST	358 AELDQVVGR	49 SAPPGPFAW	406 NTSVLGYHI
320 VPATITDIFG	343 LLLFTRYPD	48 RSAPPGPFA	399 IPHATTANT
311 GGARLDLENV	342 LLLLFTRYP	38 RLLRQRRRQ	383 AFLYEAMRF
304 AAGDSHGGGA	318 ENVPATITD	4 SLSPNDPWP	378 LPYVLAFLY
302 KKAAGDSHGG	315 LDLENVPAT	527 ELLDSAVQN	366 RDRLPCMGD
298 LSAEKKAAGD	301 EKKAAGDSH	517 KVNVTLRES	353 QTRVQAELD
293 MDAFILSAEK	290 RDMMDAFIL	513 PKSFKVNV	349 YPDVQTRVQ
287 AAPRDMMDAF	284 RPGAAPRDM	471 IGEELSKMQ	342 LLLLFTRYP
285 PGAAPRDMMD	281 ESLRPGAAP	463 FSVGKRRCI	341 WLLLLFTRY
235 VGAGSLVDVM	270 NFILDKFLR	411 GYHIPKDTV	319 NVPATITDI
205 MSAVCFGCY	246 WLQYFPNPV	403 TTANTSVLG	272 ILDKFLRHC
198 VAVANVMSA	224 LLSHNEEFG	384 FLYEAMRFS	268 FSNFILDKF
187 DGAFLDPRPL	189 AFLDPRPLT	358 AELDQVVGR	252 NPVRTVFRE
184 GSADGAFLDP	167 EGHVLSEAR	356 VQAELDQVV	246 WLQYFPNPV
177 LVALLVRGSA	163 RQVLEGHVL	350 PDVQTRVQA	244 MPWLQYFPN
172 SEARELVALL	155 FFTRQPRSR	318 ENVPATITD	231 FGRTVGAGS
147 AAHSMMRNFF	146 RAAHSMMRN	306 GDSHGGGAR	213 RYSHDDPEF
145 RRAHSMMRN	139 EHWKVQRRR	298 LSAEKKAAG	202 ANVMSAVCF
131 SMAFGHYSEH	121 ASFRVVS	286 GAAPRDMMD	194 RPLTVVAVA
117 RPAFASFRVV	116 DRPAFASFR	283 LRPGAAPRD	156 FTRQPRSRQ
111 GSAFADRPAP	100 ERAIHQALV	247 LQYFPNPVR	143 VQRRAAHSM
104 HQALVQQGSA	72 LSFARLARR	235 VGAGSLVDV	128 GGRSMAFGH
100 ERAIHQALVQ	55 FAWPLIGNA	234 TVGAGSLVD	96 VLNGERAIH
76 RLARRYGDVF	50 APPGPFAWP	229 EEFGRTVGA	93 PIVVLNGER
73 SFARLARRYG	13 LNPLSIQQT	198 VAVANVMS	92 CPIVVLNGE
69 AAHLSFARLA	531 SAVQNLQAK	195 PLTVVAVAN	79 RRYGDVFQI
67 GQAAHLSFAR	511 IKPKSFKVN	193 PRPLTVVAV	66 VGQAAHLSF
64 AAVGQAAHLS	462 IFSVGKRRC	190 FLDPRPLTV	58 PLIGNAAV
61 GNAAAVGQAA	446 LDKDGLINK	189 AFLDPRPLT	53 GPFAPWPLIG
54 PFAWPLIGNA	435 PNPNFDP	187 DGAFLDPRP	49 SAPPGPFAW
48 RSAPPGPFAW	430 DPLKWPNE	184 GSADGAFLD	43 RRRQLRSAP
29 VLATVHVQQR	414 IPKDTVVFV	177 LVALLVRGS	26 LLSVLATVH
531 SAVQNLQAKE	387 EAMRFSSFV	164 QVLEGHVLS	10 PWPLNPLSI
500 PAKMNFSGYGL	373 GDQPNLPYV	146 RAAHSMMRN	9 DPWPLNPLS
494 RANPNEP	347 TRYPDVQTR	136 HYSEHWKVQ	503 MNFSYGLTI
487 LAHQCDFRAN	293 MDAFILSAE	125 VVSGGRSMA	497 PNEPAKMNF
442 PARFLDKDGL	278 RHCESLRPG	120 FASFRVVS	478 MQLFLFISI
404 TANTSVLGYH	266 RNFSNFIL	118 PAFASFRVV	470 CIGEELSKM
401 HATTANTSVL	262 EQLNRNFSD	111 GSAFADRP	441 DPARFLDKD
387 EAMRFSSFVP	245 PWLQYFPNP	95 VVLNGERAI	437 PENFDPARF
382 LAFLYEAMRF	226 SHNEEFGR	87 IRLGSCPIV	432 LKWPNPENF
357 QAELDQVVGR	219 PEFRELLSH	82 GDVFQIRLG	430 DPLKWPNE
337 TALQWLLLLF	193 PRPLTVVAV	63 AAAGVQAAH	401 HATTANTSV
329 GASQDTLSTA	185 SADGAFLDP	60 IGNAAVQ	388 AMRFSSFVP
321 PATITDIFGA	138 SEHWKVQRR	37 QRLLRQRR	387 EAMRFSSFV
312 GARLDLENV	133 AFGHYSEHW	36 QRLLRQRR	369 LPCMGDQPN
299 SAEKKAAGDS	122 SFRVVS	26 LLSVLATVH	368 RLPCMGDQP
294 DAFILSAEKK	118 PAFASFRVV	534 QNLQAKETC	357 QAELDQVVG

236 GAGSLVDVMP	103 IHQALVQQG	531 SAVQNLQAK	343 LLLFTRYPD
206 SAVCFGCRY	92 CPIVVLNGE	515 SFKVNVTLR	296 FILSAEKKA
201 VANVMSAVCF	90 GSCPIVVLN	512 KPKSFKNV	289 PRDMMDAFI
199 VAVANVMSAV	79 RRYGDVFQI	510 TIKPKSFKV	284 RPGAAPRDM
188 GAFLDPRPLT	500 PAKMNFSYG	509 LTIKPKSFK	242 DVMPWLQYF
185 SADGAFLDPR	498 NEPAKMNFS	507 YGLTIKPKS	236 GAGSLVDVM
178 VALLVRGSAD	480 LFLFISILA	499 EPAKMNFSY	224 LLSHNEEFG
173 EARELVALLV	478 MQLFLFISI	492 DFRANPNP	206 SAVCFGCRY
132 MAFGHYSEHW	476 SKMQLFLFI	487 LAHQCDFRA	201 VANVMSAVC
120 FASFRVVS	449 DGLINKDLT	486 ILAQCDFR	199 VAVANVMSA
118 PAFASFRVVS	422 VNQWSVNH	466 GKRRIGEE	185 SADGAFLDP
114 FADRPASF	416 KDTVVFVNQ	457 TSRVMIFSV	181 LVRGSADGA
112 SAFADRPFA	392 SSFVPVTIP	454 KDLTSRVM	180 LLVRGSADG
105 QALVQQGSAF	345 LFTRYPDVQ	439 NFDPARFLD	178 VALLVRGSA
101 RAIHQALVQQ	330 ASQDTLSTA	436 NPENFDPAR	161 RSRQVLEGH
77 LARRYGDVFQ	298 LSAEKKAAG	431 PLKWPNPEN	151 MMRNFFTRQ
74 FARLARRYGD	292 MMDAFILSA	421 FVNQWSVNH	148 AHSMRNFF
55 FAWPLIGNAA	287 AAPRDMMDA	416 KDTVVFVNQ	144 QRRAAHSM
49 SAPPGPFAWP	248 QYFPNPVRT	415 PKDTVVFVN	117 RPAFAFRV
30 LATVHVGQRL	218 DPEFRELLS	397 VTIPHATTA	114 FADRPASF
532 AVQNLQAKET	199 VAVANVMSA	394 FVPVTIPHA	88 RLGSCPIVV
501 AKMNFSYGLT	166 LEGHVLSEA	392 SSFVPVTIP	63 AAVGQAAH
495 ANPNEPAKM	161 RSRQVLEGH	375 QPNLPYVLA	55 FAWPLIGNA
488 AHQCDFRANP	160 PRSRQVLEG	367 DRLPCMGDQ	52 PGPFAPWLI
443 ARFLDKDGLI	127 SGGRSMAFG	362 QVVGRDRLP	50 APPGPFAWP
405 ANTSVLGYHI	120 FASFRVVS	360 LDQVGRDR	47 RRSAPPGF
402 ATTANTSVLG	109 QQGSADFAR	348 RYPDVQTRV	42 QRRQLRSA
388 AMRFSSFPV	91 SCPIVVLNG	346 FTRYPDVQT	38 RLLRQRRRQ
383 AFLYEAMRFS	80 RYGDVFQIR	345 LFTRYPDVQ	30 LATVHVGQR
358 AELDQVGRD	67 GQAAHLSFA	329 GASQDTLST	25 LLSVLATV
338 ALQWLLLLFT	61 GNAAAVGQA	323 TITDIFGAS	14 NPLSIQTT
330 ASQDTLSTAL	42 QRRRQLRSA	316 DLENVPATI	12 PLNPLSIQQ
322 ATITDIFGAS	35 VGQRLLRQR	313 ARLDLENVP	11 WPLNPLSIQ
313 ARLDLENVPA	513 PKSFKVNV	311 GGARLDLEN	506 SYGLTIKPK
305 AGDSHGGGAR	502 KMNFSYGLT	282 SLRPGAAPR	494 RANPNEPAK
300 AEKKAAGDSH	488 AHQCDFRAN	281 ESLRPGAAP	483 FISILAHQC
295 AFILSAEKKA	469 RCIGEELSK	280 CESLRPGA	461 MIFSVGKRR
288 APRDMMDAFI	466 GKRRIGEE	279 HCESLRPGA	404 TANTSVLGY
237 AGSLVDVMPW	458 SRVMIFSVG	271 FILDKFLRH	398 TIPHATTAN
207 AVCFGCRYSH	457 TSRVMIFSV	259 REFEQLNRN	382 LAFLYEAMR
202 ANVMSAVCFG	452 INKDLTSRV	252 NPVRTVFRE	329 GASQDTLST
189 AFLDPRPLTV	440 FDPARFLDK	251 PNPVRTVFR	323 TITDIFGAS
186 ADGAFLDPRP	427 VNHDPLKWP	238 GSLVDVMPW	294 DAFILSAEK
179 ALLVRGSADG	415 PKDTVVFVN	237 AGSLVDVMP	132 MAFGHYSEH
174 ARELVALLVR	412 YHIPKDTGV	230 EFGRTVGAG	105 QALVQQGSA
148 AHSMRNFF	405 ANTSVLGYH	214 YSHDDPEFR	102 AIHQALVQQ
133 AFGHYSEHWK	375 QPNLPYVLA	207 AVCFGCRY	68 QAAHLSFAR
121 ASFRVVS	356 VQAELDQVV	201 VANVMSAVC	62 NAAAVGQAA
115 ADRPASF	340 QWLLLLFTR	200 AVANVMSAV	533 VQNLQAKET
106 ALVQQGSAFA	339 LQWLLLLFT	194 RPLTVVAVA	525 SMELLSAV
102 AIHQALVQQG	312 GARLDLENV	191 LDPRPLTVV	524 ESMELLSA
78 ARRYGDVFQI	286 GAAPRDMMD	175 RELVALLVR	487 LAHQCDFRA
75 ARLARRYGDV	283 LRPGAAPRD	171 LSEARELVA	471 IGEELSKMQ
70 AHLSEFARLAR	252 NPVRTVFRE	170 VLSEARELV	451 LINKDLTSR
65 AVGQAAHLSF	244 MPWLQYFPN	167 EGHVLSEAR	392 SSFVPVTIP
56 AWPLIGNAAA	238 GSLVDVMPW	165 VLEGHVLE	326 DIFGASQDT
50 APPGPFAWPL	208 VCFGCRYSH	160 PRSRQVLEG	321 PATITDIFT
31 ATVHVGQRL	205 MSAVCFGCR	155 FFTRQPRSR	315 DLENVPAT

HLA-A*0203 Nonamers

Pos 123456789

62 NAAAVGQAA
113 AFADRPAPA
530 DSAVQNLQA
493 FRANPNPA
287 AAPRDMMDA
111 GSAFADRP
67 GQAAHLSFA
61 GNAAAVGQA
48 RSAPPGPFA
487 LAHQCDPFA
199 VAVANVMSA
178 VALLVRGSA
105 QALVQQGSA
55 FAWPLIGNA
330 ASQDTLSTA
322 ATITDIFGA
305 AGDSHGGGA
70 AHLSEARLA
56 AWPLIGNAA
524 ESMELLDPA
480 LFLFISILA
435 PNPENFDPA
397 VTIPHATTA
394 FVPVTIPHA
380 YVLAFLYEA
375 QPNLPHYVA
350 PDVQTRVQA
314 RLDLENVPA
297 ILSAEKKA
296 FILSAEKKA
292 MMDAFILSA
280 CESLRPGAA
279 HCESLRPGA
229 EEFGRTVGA
194 RPLTVVAVA
192 DPRPLTVVA
181 LVRGSADGA
171 LSEARELVA
166 LEHVLSEA
140 HWKVQRRRA
139 EHWKVQRRRA
125 VVSGGRSMA
107 LVQQGSAFA
98 NGERAIHQA
94 IVVLNGERA
57 WPLIGNAAA
42 QRRRQLRSA
23 LLLLLSVLA
63 AAAGVQAAH
303 KAAGDSHGG
286 GAAPRDMMD
146 RAAHSMMRN
68 QAAHLSFAR
200 AVANVMSAV

194 RPLTVVAVA

191 LDPRLTVV
151 MMRNFFTRQ
98 NGERAIHQA
82 GDVFQIRLG
30 LATVHVQQR
11 WPLNPLSIQ
523 RESMELLD
512 KPKSFKVNV
506 SYGLTIKPK
505 FSYGLTIKPK
494 RANPNPAK
491 CDFRANPNE
477 KMQLFLFIS
471 IGEELSKMQ
429 HDPLKWPNP
428 NHDPLKWP
407 TSVLGYHIP
382 LAFLYEAMR
379 PYVLAFLYE
325 TDIFGASQD
310 GGGARLDLE
303 KAAGDSHGG
299 SAEKKAAGD
279 HCESLRPGA
186 ADGAFLDPR
175 RELVALLVR
150 SMMRNFFTR
108 VQQGSAFAD
87 IRLGSCPIV
85 FQIRLGSCP
49 SAPPGPFAW
48 RSAPPGPFA
43 RRRQLRSAP
7 PNPDWPLNP
1 MGTSLSPND
525 SMELLDPAV
503 MNFSYGLTI
496 NPNEPAKMN
489 HQCDFRANP
484 ISILAHQCD
463 FSVGKRRCI
454 KDLTSRVM
365 GRDLPCMG
350 PDVQTRVQA
348 RYPDVQTRV
328 FGASQDTLS
311 GGARLDLEN
305 AGDSHGGGA
304 AAGDSHGGG
302 KKAAGDSHG
215 SHDDPEFRE
168 GHVLSEARE
157 TRQPRSRQV
153 RNFFTRQPR
145 RRAAHSMMR
141 WKVQRRRAH
140 HWKVQRRRA

154 NFFTRQPRS

141 WKVQRRRAH
138 SEHWKVQRR
123 FRVVSGGRS
117 RPAFASFRV
113 AFADRPAPA
110 QGSAFADRP
102 AIHQALVQQ
88 RLGSCPIVV
78 ARRYGDVVFQ
74 FARLARRYG
71 HLSFARLAR
61 GNAAAVGQA
58 PLIGNAAAV
55 FAWPLIGNA
43 RRRQLRSAP
34 HVGQRLLRQ
29 VLATVHVQ
28 SVLATVHVG
9 DPWPLNPLS
7 PNPDWPLNP
6 SPNDPWPLN
2 GTSLSPNDP
530 DSAVQNLQA
526 MELLDPAVQ
525 SMELLDPAV
524 ESMELLDPA
516 FKVNVTLRE
504 NFSYGLTIK
496 NPNEPAKMN
493 FRANPNPA
489 HQCDFRANP
484 ISILAHQCD
481 FLFISILAH
464 SVGKRRCI
461 MIFSVGKRR
459 RVMIFSVGK
458 SRVMIFSVG
456 LTRVMIFS
450 GLINKDLTS
449 DGLINKDLT
447 DKDGLINKD
446 LDKDGLINK
435 PNPENFDPA
434 WPNPENFDPA
430 DPLKWPNP
427 VNHDPLKWP
420 VVFNQWSVN
419 VVFNQWSV
417 DTVVFNQW
409 VLGYPHIPK
407 TSVLGYHIP
406 NTSVLGYHI
404 TANTSVLGY
399 IPHATTANT
398 TIPHATTAN
396 VPTIPHATT
395 VPTIPHAT

304 AAGDSHGGG

303 KAAGDSHGG
287 AAPRDMMDA
230 EFGRTVGAG
226 SHNEEFGR
198 VAVANVMS
193 PRPLTVVAV
167 EGHVLSEAR
146 RAAHSMMRN
136 HYSEHWKVQ
118 PAFASFRVV
101 RAIHQALVQ
59 LIGNAAAVG
394 FVPVTIPHA
356 VQAELOQV
281 ESLRPGAAP
238 GSLVDVMPW
227 HNEEFGRTV
164 QVLEGHVLS
162 SRQVLEGHV
91 SCPIVVNLG
90 GSCPIVVNL
28 SVLATVHVG
530 DSAVQNLQA
517 KVNVTRES
511 IKPKSFKVN
493 FRANPNPA
484 ISILAHQCD
462 IFSVGKRR
460 VMIFSVGKR
458 SRVMIFSVG
435 PNPENFDPA
427 VNHDPLKWP
426 SVNHDPLKW
422 VNQWSVNHD
421 FVNQWSVN
419 VVFNQWSV
417 DTVVFNQW
416 KDTVVFNQ
408 SVLGYHIPK
393 SFVPVTIPH
358 AELDQVVG
318 ENVPATID
311 GGARLDLEN
308 SHGGGARLD
306 GDSHGGGAR
278 RHCESLRPG
261 FEQLNRNFS
259 REFEQLNRN
254 VRTVFREFE
237 AGSLVDVMP
235 VGAGSLVDV
222 RELLSHNE
221 FRELLSHNE
215 SHDDPEFRE
196 LTVVAVANV
177 LVALLVRGS
168 GHVLSEARE

119 AFASFRVVS	104 HQALVQQGS	393 SFVPVTIPH	160 PRSRQVLEG
499 EPAKMNFSY	101 RAIHQALVQ	389 MRFSSFPV	150 SMMRNFFTR
486 ILAHQCDFR	97 LGERAIHQ	388 AMRFSFPV	139 EHWKVQRR
441 DPARFLDKD	68 QAAHLSFAR	385 LYEAMRFSS	134 FGHYSEHWK
403 TTANTSVLG	63 AAVGQAAH	380 YVLAFLYEA	131 SMAFGHYSE
400 PHATTANTS	62 NAAAVGQAA	372 MGDQPNLPY	127 SGRSMAFG
386 YEAMRFSSF	36 GQRLLRQRR	371 CMGDQPNLP	123 FRVVS GGRS
381 VLAFLYEAM	33 VHVGRLLR	365 GRDLR LCMG	108 VQQGSAFAD
356 QAELDQVV	533 VQNLQAKET	354 TRVQAELDQ	104 HQALVQQGS
336 STALQWLL	507 YGLTIKPKS	351 DVQTRVQAE	103 IHQALVQQG
328 FGASQDTLS	487 LAHQCD FRA	342 LLLLFTRY	100 ERAIHQALV
320 VPATITDIF	465 VGKRR CIGE	341 WLLLLFTRY	94 IVVLNGERA
311 GGARLDLEN	436 NPENFD PAR	330 ASQDTLSTA	82 GDFVQIRLG
304 AAGDSHGGG	434 WPNPENFDP	325 TDIFGASQD	73 SFARLARRY
302 KKAAGDSHG	399 IPHATTANT	324 ITDIFGASQ	61 GNAAAVGQA
298 LSAEKKAAG	371 CMGDQPNLP	317 LENVPATIT	60 IGNAAAVGQ
293 MDAFILSAE	366 RDRLPCMGD	314 RLDLENVPA	56 AWPLIGNAA
285 PGAAPRDM	349 YPDVQTRVQ	303 KAAGDSHGG	27 LSVLATVHV
235 VGAGSLVDV	332 QDTLSTALQ	302 KKAAGDSHG	13 LNPLSIQQT
205 MSAVCFGCR	329 GASQDTLST	299 SAEKKAAGD	2 GTSLSPNDP
198 VAVANVMS	313 ARLDLENVP	293 MDAFILSAE	526 MELLDSAVQ
187 DGAFLDPRP	308 SHGGGARLD	277 LRHCESLRP	518 VNVTLRESM
184 GSADGAFLD	300 AEKKAAGDS	267 NFSNFILDK	516 FKVNVTLRE
177 LVALLVRGS	289 PRDMMDAFI	261 FEQLNRNFS	505 FSYGLTIK
172 SEARELVAL	273 LDKFLRHCE	254 VRTVREFE	504 NFSYGLTIK
147 AAHSMMRNF	251 PNPVRTVFR	245 PWLQYFPNP	491 CDFRANPNE
145 RRAAHSMMR	243 VMPWLQYFP	240 LVDVMPWLQ	489 HQCDFRANP
131 SMAFGHYSE	237 AGSLVDVMP	224 LLSHNEEFG	488 AHQCDFRAN
117 RPAFASFRV	231 FGRTVGAGS	220 EFRELLSHN	477 KMQLFLFIS
104 HQALVQQGS	227 HNEEFGRTV	208 VCFGCRYSH	459 RVMIFS V GK
100 ERAIHQALV	222 RELLSHNEE	206 SAVCFGCRY	453 NKDLTSRVM
76 RLARRYGDV	221 FRELLSHNE	205 MSAVCFGCR	447 DKDGLINKD
73 SFARLARRY	184 GSADGAFLD	199 VAVANVMSA	423 NQWSVNHDP
69 AAHLSFARL	162 SRQVLEGHV	196 LTVVAVANV	420 VFNQWSVN
64 AAVGQAAHL	159 QPRSRQVLE	179 ALLVRGSAD	418 TVVFNQWS
54 PFAWPLIGN	137 YSEHWKVQR	159 QPRSRQVLE	415 PKD TVVFN
29 VLVATVHVQ	136 HYSEHWKVQ	152 MRNFFTRQP	411 GYHIPKDTV
531 SAVQNLQAK	135 GHYSEHWKV	151 MMRNFFTRQ	410 LGYHIPKDT
500 PAKMNFSYG	131 SMAFGHYSE	150 SMMRNFFTR	407 TSVLGYHIP
494 RANPNPEPAK	128 GGRSMAFGH	132 MAFGHYSEH	403 TTANTSVLG
442 PARFLDKDG	123 FRVVS GGRS	131 SMAFGHYSE	397 VTIPHATTA
404 TANTSVLGY	117 RPAFASFRV	129 GRSMAGHY	390 RFSSFPVPT
401 HATTANTSV	114 FADRP AFAS	114 FADRP AFAS	389 MRFSSFPV
387 EAMRFSSFV	105 QALVQQGSA	108 VQQGSAFAD	380 YVLAFLYEA
382 LAFLYEAMR	60 IGNAAAVGQ	107 LVQQGSAFA	379 PYVLAFLYE
357 QAELDQVVG	57 WPLIGNAAA	101 RAIHQALVQ	373 GDQPNLPYV
337 TALQWLLLL	56 AWPLIGNAA	100 ERAIHQALV	372 MGDQPNLPY
329 GASQDTLST	53 GPF AWPLIG	98 NGERAIHQA	365 GRDLR LCMG
321 PATITDIFG	52 PGPF AWPLI	96 VLNGERAIH	363 VVGRDLRPC
312 GARLDLENV	45 RQLRSAPPG	93 PIVVLNGER	360 LDQVVGRDR
299 SAEKKAAGD	27 LSVLATVHV	83 DVFQIRLGS	350 PDVQTRVQA
294 DAFILSAEK	14 NPLSIQQT	79 RRYGDVFI	347 TRYPDVQTR
236 GAGSLVDVM	10 PWPLNPLSI	72 LSFARLARR	340 QWLLLLFTR
206 SAVCFGCRY	6 SPNDPWPLN	68 QAAHLSFAR	339 LQWLLLLFT
201 VANVMSAVC	534 QNLQAKETC	67 GQAAHLSFA	332 QDTLSTALQ
188 GAFLDPRPL	526 MELLDSAVQ	62 NAAAVGQAA	328 FGASQDTLS
185 SADGAFLDP	522 LRESMELL	59 LIGNAAAVG	324 ITDIFGASQ
173 EARELVALL	516 FKVNVTLRE	57 WPLIGNAAA	322 ATITDIFGA
132 MAFGHYSEH	493 FRANPNEPA	54 PFAWPLIGN	317 LENVPATIT

120 FASFRVVS
118 PAFASFRVV
114 FADRPAFAS
112 SAFADRPAF
101 RAIHQALVQ
77 LARRYGDVF
74 FARLARRYG
49 SAPPGPFAW
30 LATVHVQQR
532 AVQNLQAKE
501 AKMNFSYGL
495 ANPNEPAKM
488 AHQCDFRAN
443 ARFLDKDGL
405 ANTSLVGYH
402 ATTANTSVL
388 AMRFSSFPV
383 AFLYEAMRF
358 AELDQVVGR
338 ALQWLLLLF
313 ARLDLENVP
300 AEKKAAGDS
295 AFILSAEKK
288 APRDMMDAF
237 AGSLVDVMP
207 AVCFGCRY
202 ANVMSAVCF
189 AFLDRPLT
186 ADGAFDPR
179 ALLVRGSAD
174 ARELVALLV
148 AHSMMRNFF
133 AFGHYSEHW
121 ASFRVVSGG
115 ADRPAFASF
106 ALVQQGSAF
102 AIHQALVQQ
78 ARRYGDVFQ
75 ARLARRYGD
65 AVGQAAHLS
50 APPGPFAWP
31 ATVHVQQL

HLA-A*0203 Decamers

Pos 1234567890

56 AWPLIGNAAA
296 FILSAEKKAA

279 HCESLRPGAA
139 EHWKVQRRRA

61 GNAAAVGQAA
55 FAWPLIGNAA
193 PRPLTVVAVA
112 SAFADRPAFA
106 ALVQQGSAFA
297 ILSAEKKAAG

490 QCDFRANPN
442 PARFLDKDG
433 KWPNPENFD
425 WSVNHDPLK
423 NQWSVNHD
401 HATTANTSV
400 PHATTANTS
395 VPTIPHAT
391 FSSFVPVTI
388 AMRFSSFPV
385 LYEAMRFSS
369 LPCMGDQPN
357 QAELDQVVG
354 TRVQAELDQ
306 GDSHGGAAR
280 CESLRPGAA
277 LRHCESLRP
258 FREFEQLNR
247 LQYFPNPVR
225 LSHNEEFGR
214 YSHDDPEFR
212 CRYSHDDPE
211 GCRYSHDDP
204 VMSAVCFG
201 VANVMSAVC
178 VALLVRGSA
152 MRNFFTRQP
134 FGHYSEHWK
111 GSAFADRP
110 QGSADFADRP
78 ARRYGDVFQ
75 ARLARRYGD
70 AHLSEFARLA
44 RRQLRSAPP
41 RQRRRQLRS
40 LRQRRRQLR
37 QRLLRQRR
3 TSLSPNDPW

HLA-A26 Decamers

Pos 1234567890
333 DTLSTALQWL

527 ELLDSAVQNL
474 ELSKMQLFLF
326 DIFGASQDTL
403 TTANTSVLGY
351 DVQTRVQAE

125 VVSGGRSMAF
83 DVFQIRLGSC

380 YVLAFLYEAM
363 VVGRDRLPCM
336 STALQWLLLL
255 RTVFREFEQL
181 LVRGSADGAF
21 TTLULLLSVL

53 GPFAWPLIG
50 APPGPFAWP
46 QLRSAPPGP
42 QRRRQLRSA
41 RQRRRQLRS
35 VGQRLLRQR
30 LATVHVQQR
27 LSVLATVHV
24 LLLLSVLAT
23 LLLLSVLA
12 PLNPLSIQQ
10 PWPLNPLSI
3 TSLSPNDPW
533 VQNLQAKET
529 LDSAVQNLQ
523 RESMELDS
522 LRESMELLD
506 SYGLTIKPK
505 FSYGLTIKPK
503 MNFSYGLTI
500 PAKMNFSYG
498 NEPAKMNFS
491 CDFRANPNE
483 FISILAHQC
476 SKMQLFLFI
469 RCIGEELSK
468 RCIGEELS
460 VMIFSVGKR
451 LINKDLTSR
445 FLDDKDGLIN
444 RFLDKDGLI
441 DPARFLDKD
433 KWPNPENFD
429 HDPLKWPNP
426 SVNHDPLKW
425 WSVNHDPLK
422 VNQWSVNHD
418 TVVFVNQWS
410 LGYHIPKDT
408 SVLGYPHIPK
387 EAMRFSSFPV
378 LPYVLAFLY
369 LPCMGDQPN

366 RDRLPCMGR
363 VVGRDRLPC
353 QTRVQAELD
344 LLFTRYPDV
343 LLLFTRYPD

340 QWLLLLFTR
328 FGASQDTLS

326 DIFGASQDT
322 ATITDIFGA
319 NVPATITDI
312 GARLDLENV
310 GGGARLDLE
304 AAGDSHGGG

295 AFILSAEKK
293 MDAFILSAE
292 MMDAFILSA
279 HCESLRPGA
270 NFILDKFLR
267 NFSNFILDK
258 FREFEQLNR
249 YFPNPVRTV
248 QYFPNPVRT
247 LQYFPNPVR
243 VMPWLQYFP
241 VDVMPWLQY
240 LVDVMPWLQ
210 FGCYSHDD
208 VCFGCRYSH
205 MSAVCFGCR
204 VMSAVCFG
203 VMSAVCFG
200 AVANVMSAV
184 GSADGAFLD
175 RELVALLVR
174 ARELVALLV
166 LEGHVLSEA
155 FFTRQPRSR
137 YSEHWKVQR
135 GHYSEHWKV
129 GRMAFGHY
125 VVSGGRSMA
121 ASFRVVSGG
119 AFASFRVVS
111 GSAFADRP
98 NGERAIHQA
87 IRLGSCPIV
85 FQIRLGSCP
67 GQAAHLSFA
35 VGQRLLRQR
33 VHVQQRLLR
21 TTLULLLSV
20 QTTLULLLS
3 TSLSPNDPW

280 CESLRPGAAP	17 SIQQTLLLL	301 EKKAAGDSH
140 HWKVQRRRAH	520 VTLRESMELL	300 AEKKAAGDS
62 NAAAVGQAAH	262 EQLNRNFSNF	294 DAFILSAEK
57 WPLIGNAAAV	240 LVDVMPWLQY	292 MMDAFILSA
529 LDSAVQNLQA	88 RLGSCPIVVL	291 DMMDAFILS
523 RESMELLD SA	65 AVGQAAHLSF	287 AAPRDMMDA
492 DFRANPNEPA	319 NVPATITDIF	274 DKFLRHCE
486 ILAHQCDFRA	267 NFSNFILDKF	273 LDKFLRHCE
479 QLFLFISILA	519 NVTLRESMEL	270 NFILDKFLR
434 WPNPENFDPA	431 PLKWPENFENF	266 RNFSNFILD
396 PVTIPHATTA	517 KVNVTLRESM	262 EQLNRNFSN
393 SFVPVTIPHA	455 DLTSRVMIFS	258 FREFEQLNR
379 PYVLAFLYEA	377 NLPYVLAFLY	257 VFREFEQLN
374 DQPNLPYVLA	176 ELVALLVRGS	255 RTVFREFEQ
349 YPDVQTRVQA	142 KVQRRRAAHSM	246 WLQYFPNPV
329 GASQDTLSTA	76 RLARRYGDVF	241 VDVMPWLQY
321 PATITDIFGA	46 QLSAPP GP	233 RTVGAGSLV
313 ARLDLENVPA	469 RCIGEELSKM	222 RELLSHNEE
304 AAGDSHGGGA	408 SVLGYHIPKD	221 FRELLSHNE
295 AFILSAEKKA	242 DVMPWLQYFP	218 DPEFRELLS
291 DMMDAFILSA	196 LTVVAVANVM	211 GCRYSHDDP
286 GAAPRDMMDA	31 ATVHVGQRLL	204 VMSAVCFGC
278 RHCESLRPGA	4 SLSPNDPWPL	203 NVMSAVCFG
228 NEEFGRTVGA	510 TIKPKSFKVN	185 SADGAFLDP
198 VVAVANVMSA	447 DKDGLINKDL	181 LVRGSADGA
191 LDPRPLTVVA	417 DTVVFNQWS	180 LLVRGSADG
180 LLVRGSADGA	413 HIPKDTVV FV	178 VALLVRGSA
177 LVALLVRGSA	322 ATITDIFGAS	174 ARELVALLV
170 VLSEARELVA	274 DKFLRHCE	166 LEGHVLSEA
165 VLEGHVLSEA	249 YFPNPVRTVF	162 SRQVLEGHV
138 SEHWKVQRRRA	198 VVAVANVMSA	161 RSRQVLEGH
124 RVVSGGRSMA	164 QVLEGHVLSE	153 RNFFTRQPR
110 QGSFAFADRP	114 FADRP AFASF	145 RRAAHSM MR
104 HQALVQQGSA	102 AIHQALVQQG	128 GGRSMAFGH
97 LNGERAIHQ	38 RLLRQRRRQL	127 SGGRSMAFG
93 PIVVLNGERA	481 FLFISILAHQ	122 SFRVVSGGR
69 AAHLSFARLA	421 FVNQWSVNHD	121 ASFRVVSGG
66 VGQAAHLSFA	385 LYEAMRFSSF	105 QALVQQGSA
60 IGNAAAVGQA	359 ELQVVGRRDR	104 HQALVQQGS
54 PFAWPLIGNA	334 TLSTALQWLL	97 LNGERAIHQ
47 LRSAPP GPFA	287 AAPRDMMDAF	92 CPIVVLNGE
41 RQRRRQLRSA	271 FILDKFLRHC	91 SCPIVVLNG
22 TLLLLLSVLA	165 VLEGHVLSEA	86 QIRLGSCPI
530 DSAVQNLQAK	146 RAAHSM MRNF	80 RYGDVFQIR
524 ESMELLD SA	128 GGRSMAFGHY	76 RLARRYGDV
493 FRANPNEP	34 HVGQRLLRQR	75 ARLARRYGD
487 LAHQCDFRAN	15 PLSIQQTLL	65 AVGQAAHLS
480 LFLFISILAH	12 PLNPLSIQQT	56 AWPLIGNAA

435 PNPENFDPAR	473 EELSKMQLFL	52 PGPFAPWPLI
397 VTIPHATTAN	472 GEELSKMQLF	45 RQLRSAPPG
394 FVPVTIPHAT	459 RVMIFSVGKR	40 LRQRRRQLR
380 YVLAFLYEAM	456 LTSRVMIFSV	25 LLLSVLATV
375 QPNLPYVLAF	454 KDLTSRVMIF	21 TTL LLLSV
350 PDVQTRVQAE	450 GLINKDLTSR	14 NPLSIQQT
330 ASQDTLSTAL	445 FLDKDG LINK	13 LNPLSIQQT
322 ATIDIFGAS	412 YHIPKDTVVF	11 WPLNPLSIQ
314 RLDLENVPAT	397 VTIPHATTAN	1 MGTSLS PND
305 AGDSHGGGAR	376 PNLPHYVLAFL	
292 MMDAFILSAE	375 QPNLPYVLAF	
287 AAPRDMMDAF	346 FTRYPDVQTR	
229 EEFGR TVGAG	340 QWLLLLL FTRY	
199 VAVANVMSAV	337 TALQWLLLLF	
194 RPLTVVAVAN	314 RLDLENVPAT	
192 DPRPLTVVAV	259 REFEQLNRNF	
181 LVRGSADGAF	252 NPVRTV FREF	
178 VALLVRGSAD	241 VDVMPWLQYF	
171 LSEARELVAL	235 VGAGSLVDVM	
166 LEGHVLSEAR	234 TVGAGSLVDV	
125 VVSGGRSMAF	229 EEFGR TVGAG	
113 AFADRPAFAS	223 ELLSHNEEF G	
111 GSAFADRPAF	220 EFRELLSHNE	
107 LVQQGS AFAD	215 SHDDPEFREL	
105 QALVQQGS AF	190 FL DPRPLTVV	
98 NGERAIHQAL	187 DGAFL DPRPL	
94 IVVLNGERAI	68 QAAHLSFARL	
70 AHL SFARLAR	20 QTTL LLLSV	
67 GQAAHLSFAR	7 PNDPWPLNPL	
48 RSAPPGPFAW	509 LTIKPKSFKV	
42 QRRRQLRSAP	496 NPNEPAKMNF	
23 LLLLSVLAT	461 MIFSVGKRRC	
531 SAVQNLQAKE	426 SVNHDPLKWP	
525 SMELLSAVQ	406 NTSVLGYHIP	
494 RANPNEPAKM	393 SFVPVTIPHA	
488 AHQCDFRANP	382 LAFLYEAMRF	
481 FLFISILAHQ	316 DLENVPATIT	
436 NPENFDPARF	230 EFGRTVGAGS	
398 TIPHATTANT	195 PLTVVAVANV	
395 VPV TIPHATT	192 DPRPLTVVAV	
381 VLAFLYEAMR	172 SEARELVALL	
376 PNLPHYVLAFL	171 LSEARELVAL	
351 DVQTRVQAE	119 AFASFRVSG	
331 SQDTLSTALQ	71 HLSFARLARR	
323 TIDIFGASQ	29 VLATVHV GQR	
315 LDLENVPATI	530 DSAVQNLQAK	
306 GDSHGGGARL	499 EPAKMNF SYG	
298 LSAEKKAAGD	478 MQLFLFISIL	
293 MDAFILSAEK	470 CIGEELSKMQ	
288 APRDMMDAFI	451 LINKDLTSRV	
281 ESLRPGAAPR	439 NFDPARFLDK	
230 EFGRTVGAGS	419 VV FVNQWSVN	
200 AVANVMSAVC	398 TIPHATTANT	
195 PLTVVAVANV	343 LLLFTRYPDV	

182 VRGSADGAFL
179 ALLVRGSADG
172 SEARELVALL
167 EGHVLSEARE

141 WKVQRRRAHS
126 VSGGRSMAFG
114 FADRPFAFASF

108 VQQGSAFADR
99 GERAHQALV
95 VVLNGERAIH
71 HLSFARLARR
68 QAAHLSFARL

63 AAAGVQAAHL
58 PLIGNAAAVG
49 SAPPGPFAWP
43 RRRQLRSAPP
24 LLLLSVLATV

HLA-A*0203 Octamers

Pos 12345678
531 SAVQNLQA
525 SMELDSA
494 RANPNEPA
488 AHQCDFRA
481 FLFISILA
436 NPENFDPA
398 TIPHATTA
395 VPVTIPHA
381 VLAFLYEA
376 PNLPYVLA

351 DVQTRVQA

331 SQDTLSTA
323 TITDIFGA
315 LDLENVPA
306 GDSHGGGA

298 LSAEKKAA
297 ILSAEKKA
293 MDAFILSA
288 APRDMMDA
281 ESLRPGAA
280 CESLRPGA
230 EFGRTVGA
200 AVANVMSA
195 PLTVVAVA

193 PRPLTVVA
182 VRGSADGA
179 ALLVRGSA
172 SEARELVA
167 EGHVLSEA
141 WKVQRRRA

324 ITDIFGASQD
323 TITDIFGASQ
270 NFILDKFLRH
260 EFEQLNRNFS

256 TVFREFEQLN
238 GSLVDVMPWL
212 CRYSHDDPEF

124 RVVSGGRSMA
111 GSAFADRPAF
72 LSFARLARRY
58 PLIGNAAAVG
24 LLLLSVLATV

23 LLLLSVLAT
498 NEPAKMNFSY
494 RANPNEPAKM
492 DFRANPNEPA
484 ISILAHQCDF
471 IGEELSKMQL

464 SVGKRRRCIGE
436 NPENFDPARF
394 FVPVTIPHAT
374 DQPNLPYVLA
362 QVVGRDRLPC
338 ALQWLLLLFT
318 ENVPATITDI
296 FILSAEKKAA
291 DMMDAFILSA
282 SLRPGAAPRD
233 RTVGAGSLVD
205 MSAVCFGCRY
203 NVMSAVCFGC

200 AVANVMSAVC

197 TVVAVANVMS
177 LVALLVRGSA
156 FTRQPRSRQV
107 LVQQGSAFAD

105 QALVQQGSAF
59 LIGNAAAVGQ
54 PFAWPLIGNA
28 SVLATVHVGG
18 IQQTLLLLLL
532 AVQNLQAKET
507 YGLTIKPKSF
483 FISILAHQCD
480 LFLFISILAH

418 TVVFNQWSV
402 ATTANTSVLG
384 FLYEAMRFSS
381 VLAFLYEAMR
371 CMGDQPNLPY
355 RVQAELDQVV

140 HWKVQRRRA
126 VSGGRSMA
114 FADRPFA
112 SAFADRPFA
108 VQQGSAFA

106 ALVQQGSA
99 GERAIHQ
95 VVLNGERA
71 HLSFARLA
68 QAAHLSFA
63 AAAVGQAA
62 NAAAVGQA
58 PLIGNAAA
57 WPLIGNAA

56 AWPLIGNA
49 SAPPGPFA
43 RRRQLRSA
24 LLLLSVLA

283 LRPGAAPRDM
222 RELLSHNEEF
218 DPEFRELLSH
216 HDDPEFRELL
207 AVCFGCRYSH

201 VANVMSAVCF
169 HVLSEARELV
157 TRQPRSRQVL
147 AAHSMMRNFF
96 VLNGERAIHQ
95 VVLNGERAIH
94 IVVLNGERAI
93 PIVVLNGERA
86 QIRLGSCPIV

63 AAAVGQAAHL
50 APPGPFAWPL
16 LSIQQTTL
528 LLDSAVQNLQ
524 ESMELLD
521 TLRESMELLD
500 PAKMNFSYGL
486 ILAHQCDFRA
485 SILAHQCDFR
482 LFISILAHQC
479 QLFLFISILA
452 INKDLTSRVM
396 PVTIPHATTA
383 AFLYEAMRFS
373 GDQPNLPYVL
369 LPCMGDQPNL
368 RLPCMGDQPN
353 QTRVQAELDQ
344 LLFTRYPDVQ
330 ASQDTLSTAL
308 SHGGGARLDL
306 GD SHGGGARL
297 ILSAEKKAAG
272 ILDKFLRHCE
253 PVRTVFREFE
208 VCFGCRYSHD
182 VRGSADGAFL
170 VLSEARELVA

143 VQRRAAHSM

106 ALVQQGSAFA
98 NGERAIHQAL
80 RYGDVFQIRL
39 LLRQRRRQLR
32 TVHVGQRLLR
30 LATVHVGQRL
26 LLSVLATVHV
2 GTSLSPNDPW
513 PKSFKVNVTL
508 GLTIKPKSFK
466 GKRRRCIGEEL
442 PARFLDKDGL

438 ENFDPARFLD
430 DPLKWPNPEN
423 NQWSVNHDPL
401 HATTANTSVL
367 DRLPCM GDQP
360 LDQVVGRDRL
301 EKKAAGDSHG
295 AFILSAEKKA
294 DAFILSAEKK
289 PRDMMDAFIL
284 RPGAAPRDMM
276 FLRHCESLRP
257 VFREFEQLNR
246 WLQYFPNPVR
239 SLVDVMPWLQ
231 FGRTVGAGSL
224 LLSHNEEFGR
217 DDPEFRELLS
180 LLVRGSADGA
179 ALLVRGSADG
168 GHVLSEAREL
154 NFFTRQPRSR
123 FRVVS GGSRM
113 AFADRP AFAS
25 LLLSVLATVH
22 TLLLLLSVLA
14 NPLSIQQTTL
9 DPWPLNPLSI
515 SFKVNVTLRE
437 PENFDPARFL

420 VFVNQWSVNH
409 VLGYPHIPKDT
390 RFSSFPVTI
389 MRFSSFPVT
345 LFTRYPDVQT
342 LLLLFTTRYPD
341 WLLLLFTTRYPD
335 LSTALQWLLL
307 DSHGGGARLD

286 GAAPRDMMDA
268 FSNFILDKFL
264 LNRNFSNFIL
263 QLNRNFSNFI
248 QYFPNPVRTV
219 PEFRELLSHN
173 EARELVALLV
167 EGHVLSEARE
162 SRQVLEGHVL
155 FFTRQPRSRQ

139 EHWKVQRRAA
116 DRPAFASFRV
101 RAIHQALVQQ
49 SAPP GPFAWP
514 KSFKVNVTLR
504 NFSYGLTIKP
503 MNFSYGLTIK

446 LDKDGLINKD
444 RFLDKDGLIN
441 DPARFLDKDG
415 PKDTVVFVNQ
372 MGDQPNLPYV
350 PDVQTRVQAE
292 MMDAFILSAE
281 ESLRPGAAPR
275 KFLRHCESLR
266 RNFSNFILDK
189 AFLDPRPLTV
185 SADGAFLDPR
145 RRAAHSMMRN
131 SMAFGHYSEH

126 VSGGRSMAFG
122 SFRVVSGGRS

108 VQQGSAFADR
100 ERAIHQALVQ
97 LGERAIHQ
90 GSCPIVVLNG
84 VFQIRLGSCP
79 RRYGDVFQIR
73 SFARLARRYG
53 GPFAWPLIGN
33 VHVQQRLLRQ
512 KPXSFKVNV
505 FSYGLTIKPK
497 PNEPAKMNFS
487 LAHQCDFRAN
465 VGKRRRCIGEE
462 IFSVGKRRCI
449 DGLINKDLTS
440 FPARFLDKD
434 WPNPENFDPA
414 IPKDTVVFVN
387 EAMRFSSFVP
361 DQVVGRDRLP
358 AELDQVVGRD
357 QAELDQVVGR
354 TRVQAELDQV
329 GASQDTLSTA
327 IFGASQDTLS
311 GGARLDLENV
309 HGGGARLDLE
251 PNPVRTVFRE
244 MPWLQYFPNP
209 CFGCRYSHDD

199 VAVANVMSAV
193 PRPLTVVAVA
184 GSADGAFLDP
175 RELVALLVRG
159 QPRSRQVLEG

137 YSEHWKVQRR
133 AFGHYSEHWK
120 FASFRVVSGG

91 SCPIVVLNGE
10 PWPLNPLSIQ
523 RESMELLDSA
522 LRESMELLDS
516 FKVNVTLRES
477 KMQLFLFISI
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475 LSKMQLFLFI
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435 PNPENFDPAR
428 NHDPLKWPNP

416 KDTVVFVNQW
388 AMRFSSFVPV
379 PYVLAFLYEA
321 PATITDIFGA
298 LSAEKKAAGD
258 FREFEQLNRN
243 VMPWLQYFPN

237 AGSLVDVMPW
225 LSHNEEFGR
160 PRSRQVLEGH
150 SMMRNFFTRQ

132 MAFGHYSEHW
117 RPAFASFVRV
89 LGSCPIVVLN
81 YGDVFQIRLG
78 ARRYGDVFQI
66 VGQAAHLSFA
60 IGNAAAVGQA
41 RQRRRQLRSA
511 IKPKSFKVVN
501 AKMNFSYGLT
404 TANTSVLGYH
391 FSSFVPVTIP
378 LPYVLAFLYE
366 RDRLPCM GDQ

356 VQAELDQVVG
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277 LRHCESLRPG
265 NRNFSNFILD
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202 ANVMSAVCFG
174 ARELVALLVR
153 RNFFTRQPRS
149 HSMMRNFFTR

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75 ARLARRYGDV
48 RSAPPGPFAW
27 LSVLATVHVG

19 QQTLLLLLS
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491 CDFRANPNP
490 QCDFRANPNE
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453 NKDLTSRVMI
365 GRDRLPCMGD
349 YPDVQTRVQA
347 TRYPDVQTRV
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325 TDIFGASQDT
315 LDLENVPATI

305 AGDSHGGGAR
300 AEKKAAGDSH
293 MDAFILSAEK
285 PGAAPRDMMD
250 FPNPVRTVFR
236 GAGSLVDVMP
188 GAFLDPRPLT

141 WKVQRRRAHS

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118 PAFASFRVVS
115 ADRPAFASFR
112 SAFADRPAPA
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55 FAWPLIGNAA
51 PPGPFAWPLI
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506 SYGLTIKPKS
495 ANPNPAKMN
488 AHQCDFRANP
463 FSVGKRRRCIG
458 SRVMIFSVGK
443 ARFLDKDGLI
432 LKWPNPENFD
405 ANTSVLGYHI
400 PHATTANTSV
392 SSFVPVTIPH
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370 PCMGDQPNLP
364 VGRDRLPCMG
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331 SQDTLSTALQ
313 ARLDLENVPA

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280 CESLRPGAAP
279 HCESLRPGAA
273 LDKFLRHCE
269 SNFILDKFLR
247 LQYFPNPVRT
228 NEEFGRTVGA
227 HNEEFGRTVG
226 SHNEEFGRTV
214 YSHDDPEFRE
194 RPLTVVAVAN
191 LDPRLTVVA
186 ADGAFLDPRP
178 VALLVRGSAD
161 RSRQVLEGHV
158 RQPRSRQVLE

144 QRRAAHSMMR
109 QQGSADFADRP

104 HQALVQQGSA
103 IHQALVQQGS
87 IRLGSCPIVV
85 FQIRLGSCPI
70 AHLSFARLAR
67 GQAAHLSFAR

64 AAVGQAAHLS
57 WPLIGNAAAV
45 RQLRSAPPGP
43 RRRQLRSAPP
42 QRRRQLRSAP
35 VGQRLLRQRR
13 LNPLSIQQT
8 NDPWPLNPLS
6 SPNDPWPLNP
5 LSPNDPWPLN
3 TSLSPNDPWP
534 QNLQAKETCQ
529 LDSAVQNLQA
525 SMELLSAVQ
489 HQCDFRANPN
468 RRCIGEELSK
433 KWPNPENFDP
429 HDPLKWPNE
427 VNHDPLKWP

425 WSVNHDPLKW
424 QSVNHDPLK
395 VPVTIPHATT
332 QDTLSTALQW
320 VPATITDIFG
310 GGGARLDLEN
299 SAEKKAAGDS
261 FEQLNRNFSN
254 VRTVFREFEQ
245 PWLQYFPNPV
232 GRTVGAGSLV
221 FRELLSHNEE

166 LEGHVLSEAR
163 RQVLEGHVLS
152 MRNFFTRQPR
151 MMRNFFTRQP

138 SEHWKVQRRR

135 GHYSEHWKVQ
134 FGHYSEHWKV
130 RSMAFGHYSE
127 SGGRSMAFGH
99 GERAHQALV
82 GDVFQIRLGS
77 LARRYGDVFQ
74 FARLARRYGD
52 PGPFAWPLIG
47 LRSAPPGPFA
44 RRQLRSAPPG
40 LRQRRRQLRS
37 QRLLRQRRRQ
36 QRLLRQRRR
11 WPLNPLSIQQ
1 MGTSLSPPNDP

**Prediction of HLA binding peptides from cytochrome P450 1B1
using the algorithm on the BIMAS website
(http://bimas.dcrt.nih.gov/molbio/hla_bind/)**

HLA-allele	peptide length	rank	starting position in the protein	sequence	score
A1	9mer	1	372	MGDQPNLPY	31.25
		2	137	YSEHWKVQR	27
	10mer	1	240	LVDVmPWLQY	125
		2	439	NFDPaRFLDK	25
A_1101	9mer	1	459	RVMIFSVGK	12
		2	408	SVLGYHIPK	6
	10mer	1	459	RVMIfSVGKR	2.4
		2	508	GLTIKPKSFK	1.2
A_0201	9mer	1	246	WLQYFPNPV	1215.769
		2	239	SLVDVMPWL	1107.961
	10mer	1	24	LLLLsVLATV	1006.209
		2	343	LLLFtRYPDV	656.223
A_0205	9mer	1	479	QLFLFISIL	84
		2	239	SLVDVMPWL	42
	10mer	1	478	MQLFIFISIL	114.24
		2	24	LLLLsVLATV	20.4
A3	9mer	1	150	SMMRNFFTR	54
		2	408	SVLGYHIPK	27
	10mer	1	508	GLTIKPKSFK	90
		2	445	FLDKdGLINK	60
A_3101	9mer	1	150	SMMRNFFTR	36
		2	460	VMIFSVGKR	8
	10mer	1	459	RVMIfSVGKR	36
		2	339	LQWLILLFTR	36
A_3302	9mer	1	72	LSFARLARR	15
		2	225	LSHNEEFGR	15
	10mer	1	281	ESLRpGAAPR	45
		2	359	ELDQvVGRDR	27
A24	9mer	1	213	RYSHDDPEF	220
		2	275	KFLRHCESL	60
	10mer	1	80	RYGDvFQIRL	480
		2	385	LYEAmRFSSF	180
A68.1	9mer	1	408	SVLGYHIPK	240
		2	459	RVMIFSVGK	240
	10mer	1	459	RVMIfSVGKR	400
		2	34	HVGQrLLRQR	400
B7	9mer	1	173	EARELVALL	120
		2	39	LLRQRRRQL	60
	10mer	1	50	APPGpFAWPL	240
		2	288	APRDmMDAFI	240
B8	9mer	1	39	LLRQRRRQL	160

		2	173	EARELVALL	48
	10mer	1	156	FTRQpRSRQV	12
		2	512	KPKStKVNVt	8
B14	9mer	1	443	ARFLDKDGL	100
		2	361	DQVVGRDRL	45
	10mer	1	38	RLLRqRRRQL	250
		2	75	ARLArRYGDV	200
B_2702	9mer	1	79	RRYGDVFQI	900
		2	443	ARFLDKDGL	300
	10mer	1	212	CRYShDDPEF	1000
		2	443	ARFLdKDGLI	300
B_2705	9mer	1	443	ARFLDKDGL	10000
		2	79	RRYGDVFQI	9000
	10mer	1	79	RRYGdVFQIR	15000
		2	468	RRCIgeELSK	6000
B40	9mer	1	229	EEFGRTVGA	80
		2	172	SEARELVAL	40
	10mer	1	473	EELSkMQLFL	40
		2	172	SEAReLVALL	40
B60	9mer	1	172	SEARELVAL	640
		2	472	GEELSKMQL	352
	10mer	1	473	EELSkMQLFL	640
		2	172	SEAReLVALL	352
B61	9mer	1	229	EEFGRTVGA	60
		2	280	CESLRPGAA	20
	10mer	1	46	QLRSaPPGPF	120
		2	377	NLPYvLAFLY	80
B62	9mer	1	338	ALQWLLLLF	96
		2	341	WLLLLFTRY	96
	10mer	1	46	QLRSaPPGPF	120
		2	377	NLPYvLAFLY	80
B_3501	9mer	1	288	APRDMMDAF	120
		2	284	RPGAAPRDM	80
	10mer	1	284	RPGAaPRDMM	80
		2	288	APRDmMDAFI	48
B_3701	9mer	1	217	DDPEFRELL	200
		2	454	KDLTSRVMI	200
	10mer	1	148	AHSMMRNFF	39
		2	428	NHDPLKWPn	11.7
B_3801	9mer	1	148	AHSMMRNFF	39
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	10mer	1	148	AHSMMRNFF	39
		2	428	NHDPLKWPn	11.7
B_3901	9mer	1	135	GHYSEHWKV	60
		2	412	YHIPKDTVv	30
	10mer	1	215	SHDDpEFREL	540
		2	168	GHVLSAREL	180
B_3902	9mer	1	19	QQTLLLLLL	24

		2	374	DQPNLPYVL	24
	10mer	1	447	DKDGIINKDL	24
		2	478	MQLFIFISIL	24
B_4403	9mer	1	473	EELSKMQLF	120
		2	386	YEAMRFSSF	80
	10mer	1	498	NEPAKMNFYS	180
		2	222	RELLSHNEEF	80
B_5101	9mer	1	414	IPKDTVVFV	314.6
		2	387	EAMRFSSFV	200
	10mer	1	9	DPWPINPLSI	1600
		2	288	APRDmMDAFI	440
B_5102	9mer	1	117	RPAFASFRV	400
		2	188	GAFLDPRPL	302.5
	10mer	1	9	DPWPINPLSI	2200
		2	57	WPLIgNAAAV	660
B_5103	9mer	1	401	HATTANTSV	121
		2	387	EAMRFSSFV	110
	10mer	1	410	LGYHiPKDTV	132
		2	199	VAVAnVMSAV	121
B_5201	9mer	1	356	VQAELDQVV	396
		2	374	DQPNLPYVL	88
	10mer	1	478	MQLFIFISIL	90
		2	117	RPAFaSFRVV	50
B_5801	9mer	1	238	GSLVDVMPW	105.6
		2	49	SAPPGPFAW	80
	10mer	1	48	RSAPpGPFAW	480
		2	146	RAAHsMMRNF	99

CLAIMS

1. A method of treating a patient that comprises or is at risk of comprising a cell that expresses cytochrome P450 1B1, said method comprising administering to said patient a cytotoxic T lymphocyte that kills said cell in a cytochrome P450 1B1-specific, major histocompatibility complex-restricted fashion.
2. The method of claim 1, wherein said cytotoxic T lymphocyte is autologous to said patient.
3. The method of claim 1, wherein said cytotoxic T lymphocyte is allogeneic to said patient.
4. The method of claim 1, wherein said cytotoxic T lymphocyte is generated by activation with an antigen presenting cell that has been pulsed with cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule.
5. The method of claim 1, further comprising administering to said patient a cytotoxic T lymphocyte that kills a cell in said patient that expresses a second tumor associated antigen.
6. The method of claim 5, wherein said second tumor associated antigen is telomerase.
7. A method of treating a patient that comprises or is at risk of comprising a cell that expresses cytochrome P450 1B1, said method comprising administering to said patient an antigen presenting cell that activates in said patient a cytotoxic T lymphocyte that kills said cell in a cytochrome P450 1B1-specific, major histocompatibility complex-restricted fashion.

8. The method of claim 7, wherein said antigen presenting cell has been pulsed with cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule,

5 9. The method of claim 7, further comprising administering to said patient an antigen presenting cell that activates in said patient a cytotoxic T lymphocyte that kills a cell in said patient that expresses a second tumor associated antigen.

10 10. The method of claim 9, wherein said second tumor associated antigen is telomerase.

11. A method of treating a patient that comprises or is at risk of comprising a cell that expresses cytochrome P450 1B1, said method comprising administering to said patient a peptide of cytochrome P450 1B1 that binds to a
15 major histocompatibility complex molecule, wherein said peptide of cytochrome P450 1B1 is processed by an antigen presenting cell in said patient, which activates a cytotoxic T lymphocyte in said patient to kill said cell that expresses cytochrome P450 1B1 in a cytochrome P450 1B1-specific, major histocompatibility complex-restricted fashion.

20

12. The method of claim 11, wherein said peptide of cytochrome P450 1B1 is administered to said patient in association with an adjuvant.

13. The method of claim 11, further comprising administering to said
25 patient a second tumor associated antigen or a peptide thereof that binds to a major histocompatibility complex molecule, wherein said second tumor associated antigen or said peptide thereof is processed by an antigen presenting cell in said patient, which activates a cytotoxic T lymphocyte in said patient to kill cells that express the second tumor associated antigen in a tumor associated
30 antigen-specific, major histocompatibility complex-restricted fashion.

14. The method of claim 13, wherein said second tumor associated antigen is telomerase.

15. A method of treating a patient that comprises or is at risk of
5 comprising a cell that expresses cytochrome P450 1B1, said method comprising administering to said patient a nucleic acid molecule encoding cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule, wherein said nucleic acid molecule is expressed in said patient so that the polypeptide or peptide it encodes can be processed by an antigen
10 presenting cell in said patient, which activates a cytotoxic T lymphocyte in said patient to kill said cell that expresses cytochrome P450 1B1 in a cytochrome P450 1B1-specific, major histocompatibility complex-restricted fashion.

16. The method of claim 15, wherein said nucleic acid molecule encoding
15 cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 is in an expression vector.

17. The method of claim 15, further comprising administering to said patient a nucleic acid molecule encoding a second tumor associated antigen or a
20 peptide thereof that binds to a major histocompatibility complex molecule, wherein said nucleic acid molecule is expressed in said patient so that the polypeptide or peptide that it encodes can be processed by an antigen presenting cell in said patient, which activates a cytotoxic T lymphocyte in said patient to kill cells that express the second tumor associated antigen in a tumor associated
25 antigen-specific, major histocompatibility complex-restricted fashion.

18. The method of claim 17, wherein the second tumor associated antigen is telomerase.

30 19. The method of claim 1, 7, 11, or 15, wherein said patient comprises a tumor comprising cells that express cytochrome P450 1B1.

20. The method of claim 4 or 7, wherein said antigen presenting cell is a dendritic cell or a CD40-activated B cell.

5 21. The method of claim 4, 8, 11, or 15, wherein said peptide of cytochrome P450 1B1 binds to a class I major histocompatibility complex molecule.

22. The method of claim 21, wherein said class I major histocompatibility
10 complex molecule is an HLA-A2 or an HLA-A3 molecule.

23. The method of claim 22, wherein said peptide of cytochrome P450 1B1 comprises the amino acid sequence of CYP239 (SEQ ID NO:1), CYP246 (SEQ ID NO:2), CYP190 (SEQ ID NO:3), or CYP528 (SEQ ID NO:4).

15 24. A method of assessing the level of immunity of a patient to cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule, said method comprising measuring the level of cytotoxic T lymphocytes specific for cytochrome P450 1B1 or said
20 peptide of cytochrome P450 1B1 in a sample from said patient.

25. The method of claim 24, wherein said sample is obtained from said patient before or after a cancer treatment is administered to said patient.

25 26. A cytochrome P450 1B1 peptide that binds to a major histocompatibility complex molecule.

27. The peptide of claim 26, consisting essentially of the amino acid
sequence of CYP239 (SEQ ID NO:1), CYP246 (SEQ ID NO:2), CYP190 (SEQ
30 ID NO:3), or CYP528 (SEQ ID NO:4).

28. An *ex vivo* generated cytotoxic T lymphocyte that specifically kills a cell expressing cytochrome P450 1B1 in a specific, major histocompatibility complex-restricted fashion.

5 29. An *ex vivo* generated antigen presenting cell that presents a peptide of a cytochrome P450 1B1 in the context of a major histocompatibility complex molecule.

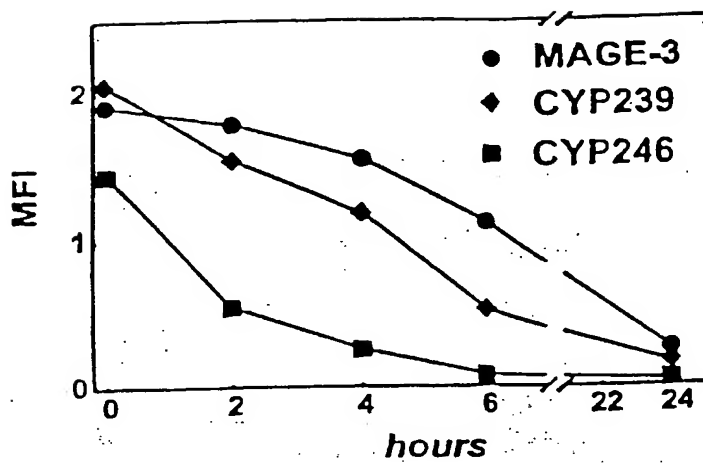
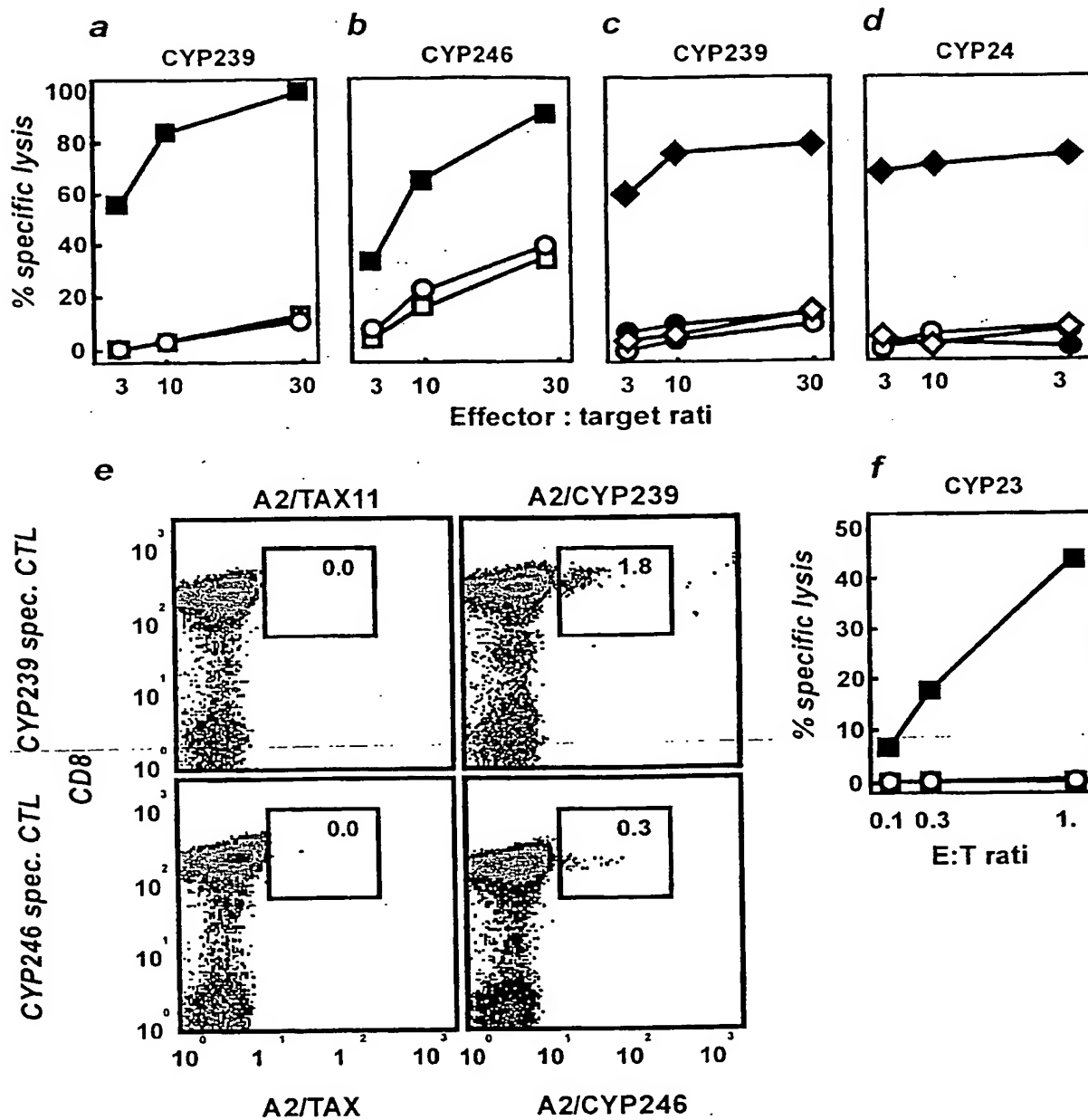


Fig. 1

FIGURE 2



**CYP239 SPECIFIC LYSIS OF PULSED CD40-B CELLS IS
DEPENDENT ON PEPTIDE CONCENTRATION**

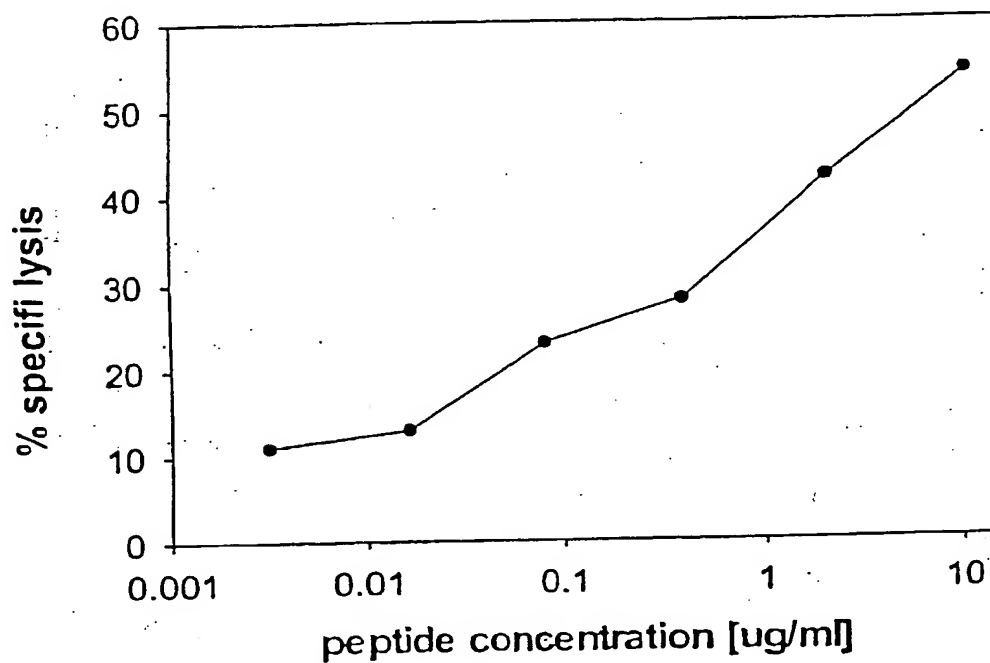
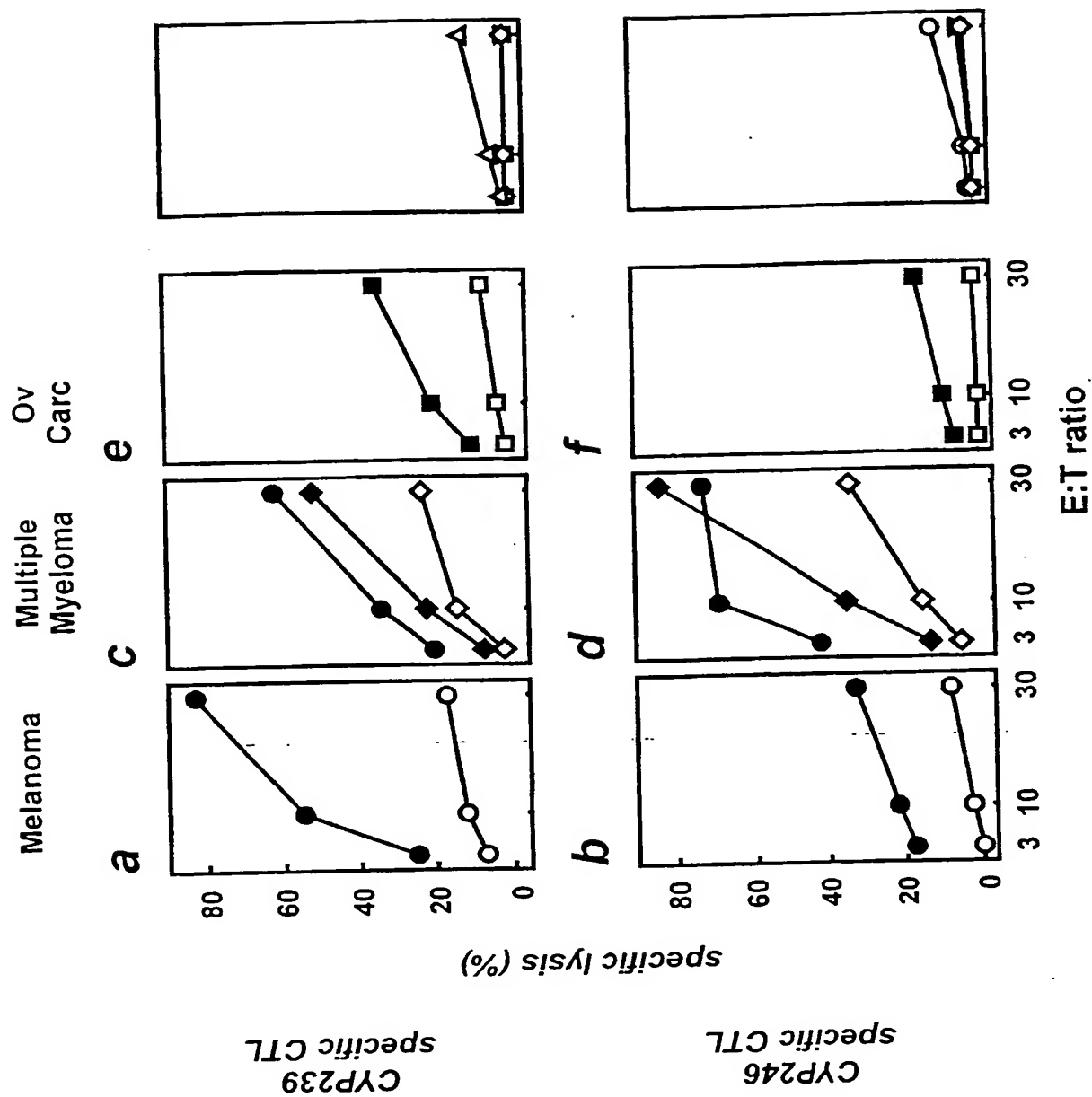


Fig. 3

FIGURE 4



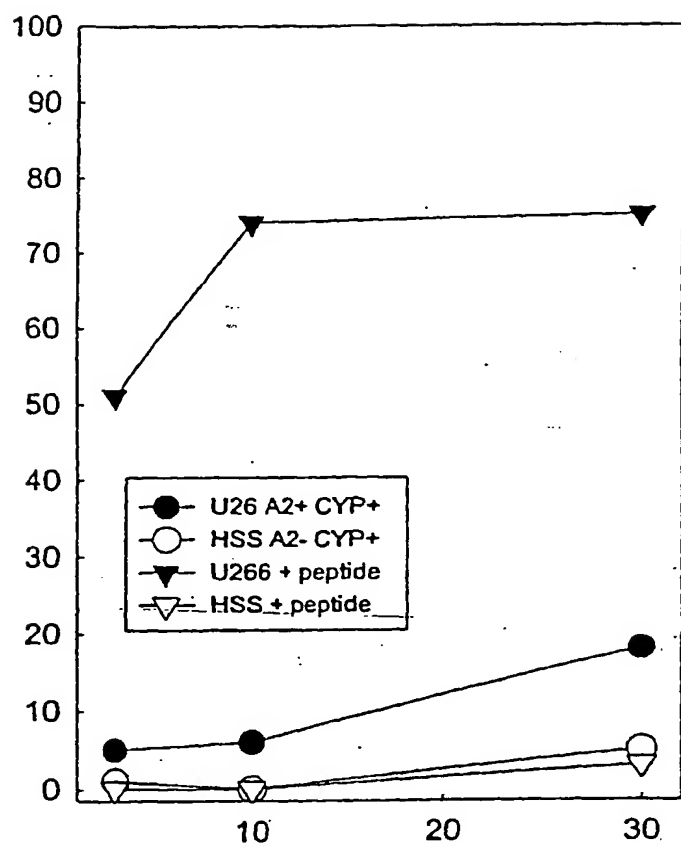
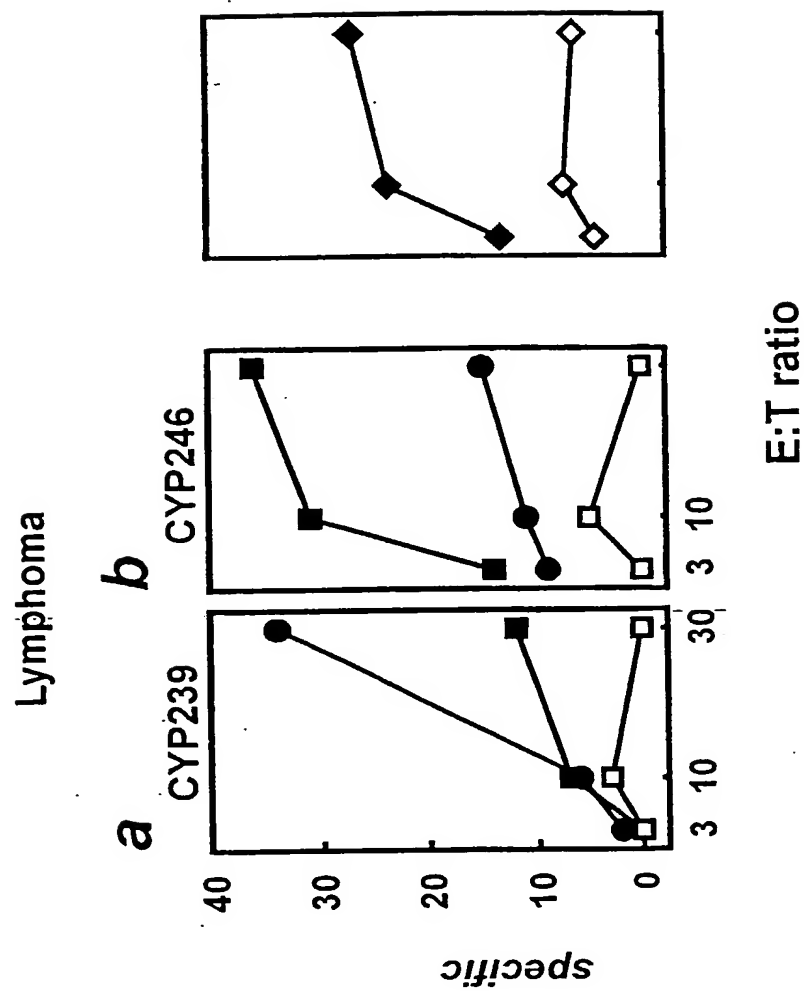


Fig. 5

FIGURE 6



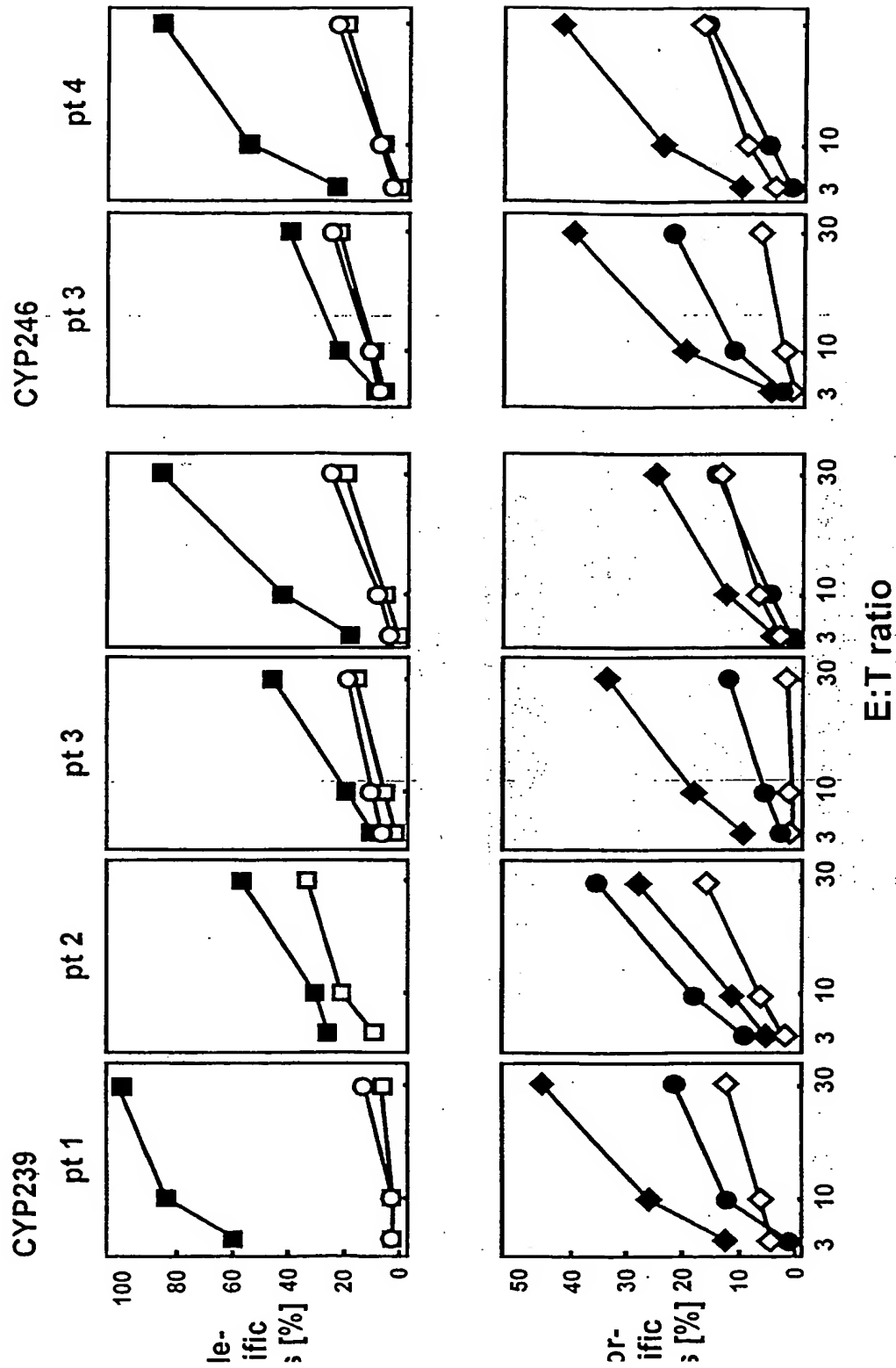
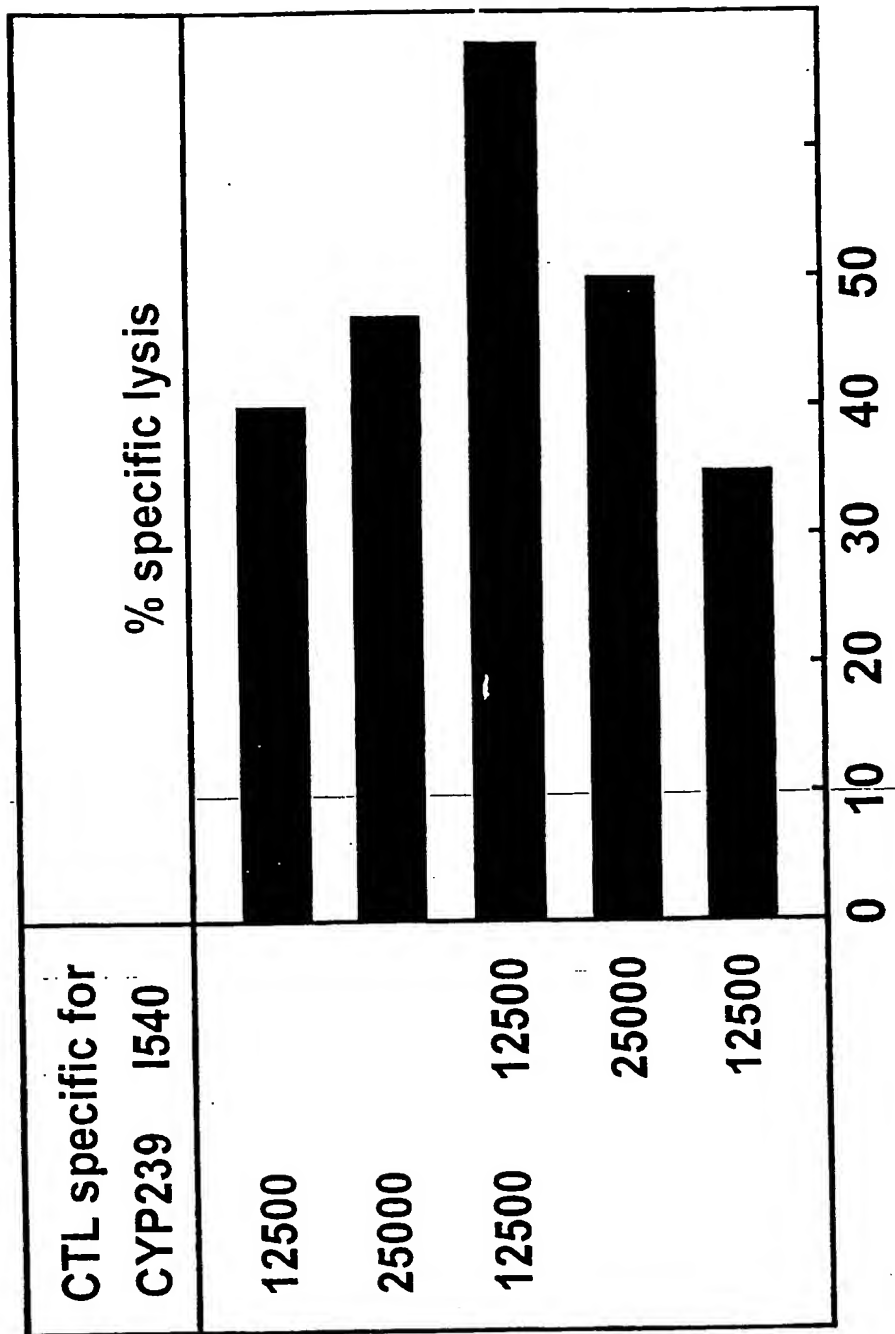


FIGURE 8



Use of heteroclitic peptides

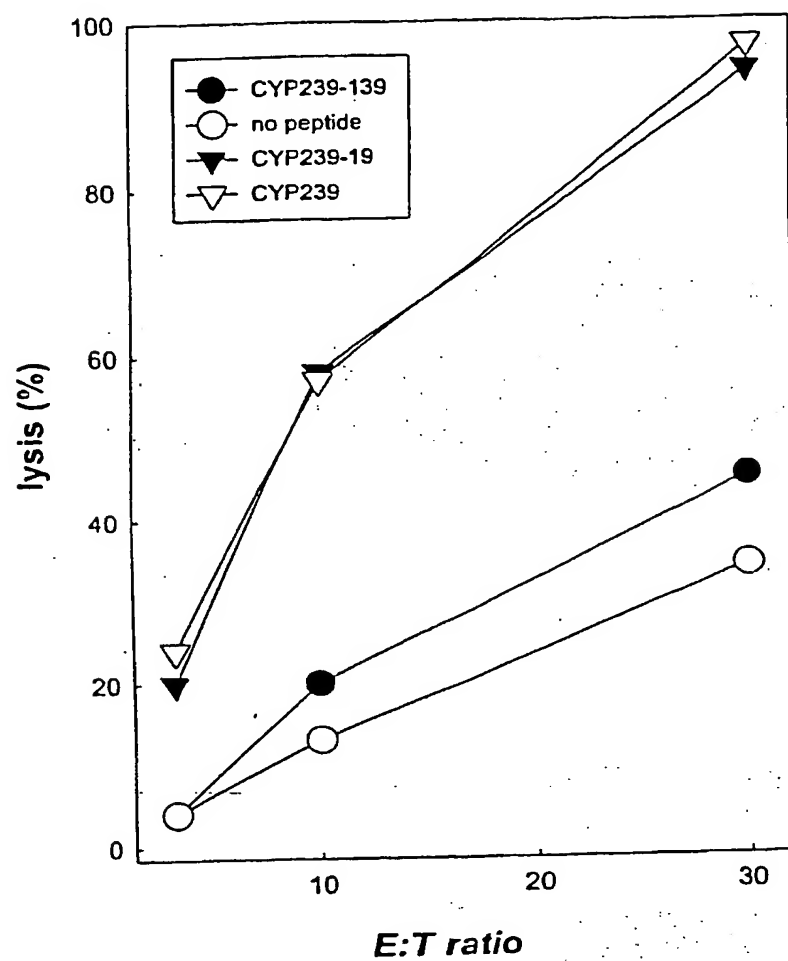


Fig. 9

FIGURE 10

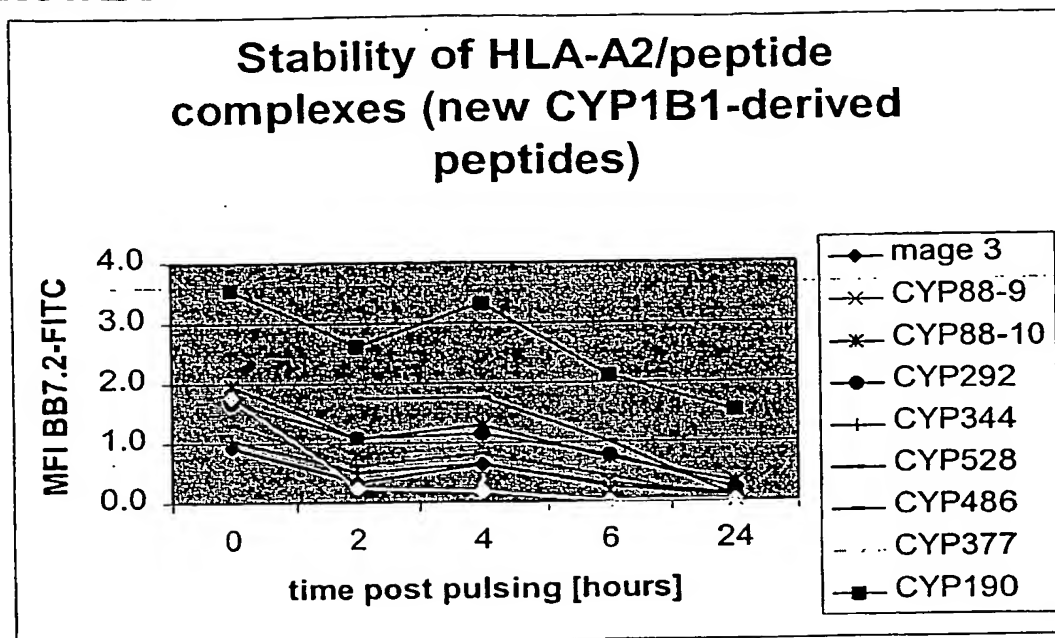


FIGURE 11

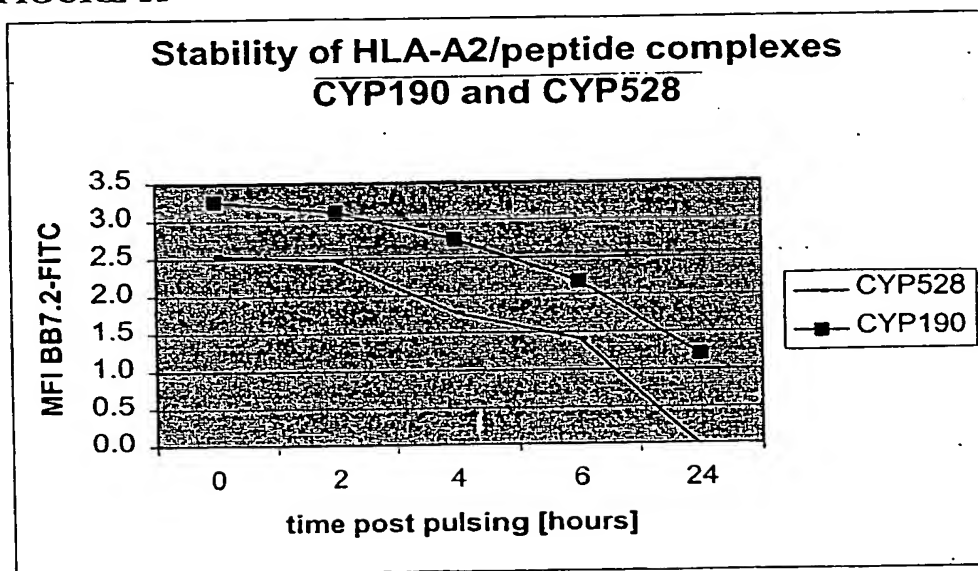


FIGURE 12A

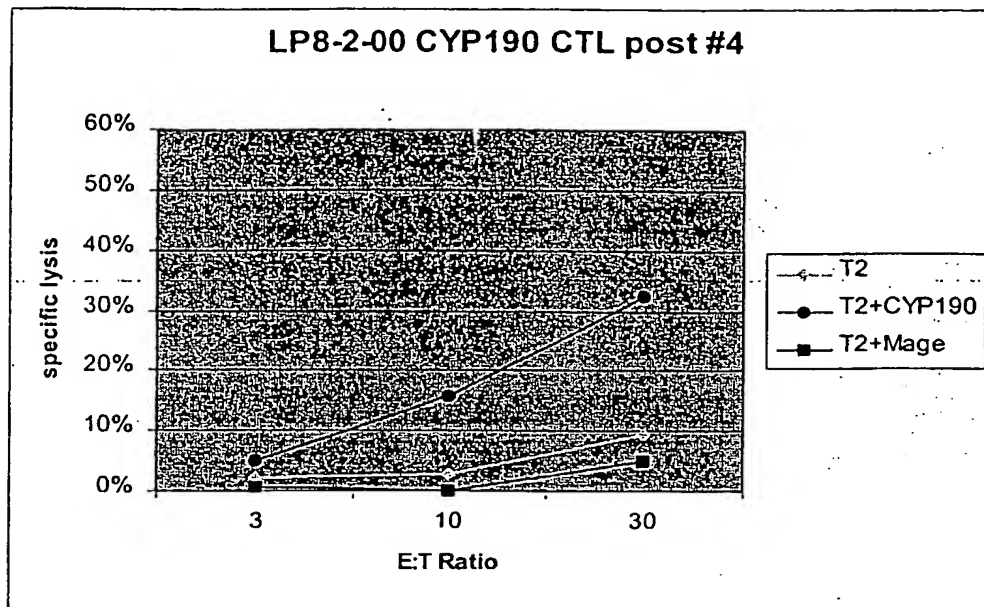
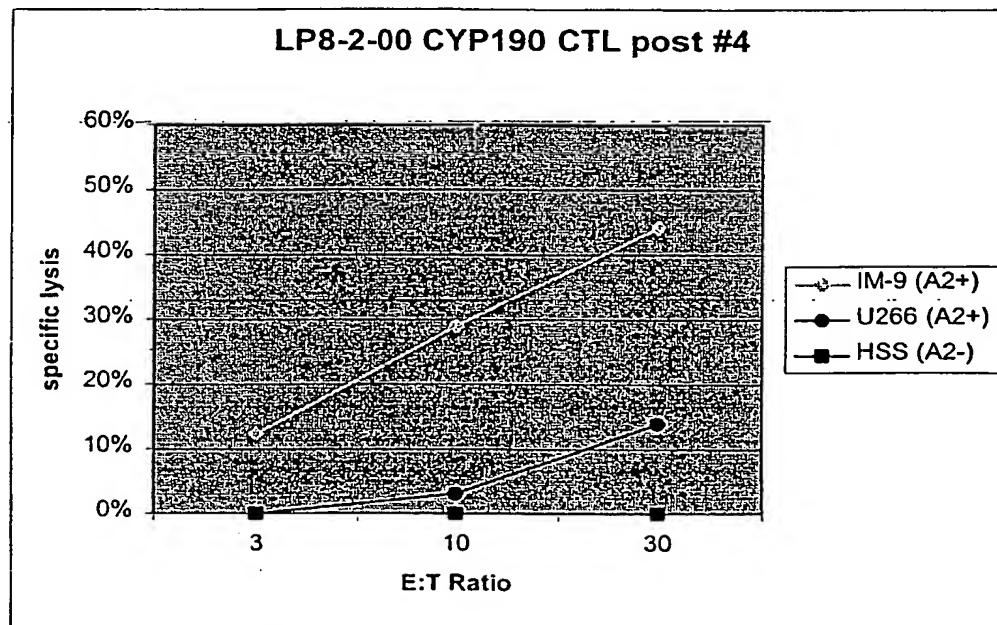


FIGURE 12B



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FIGURE 12C

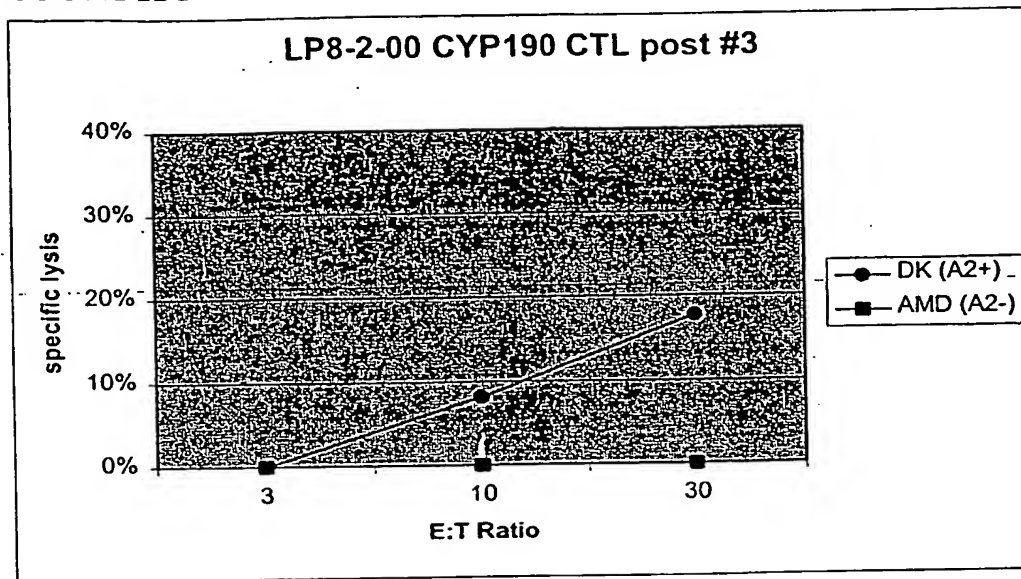


FIGURE 13A

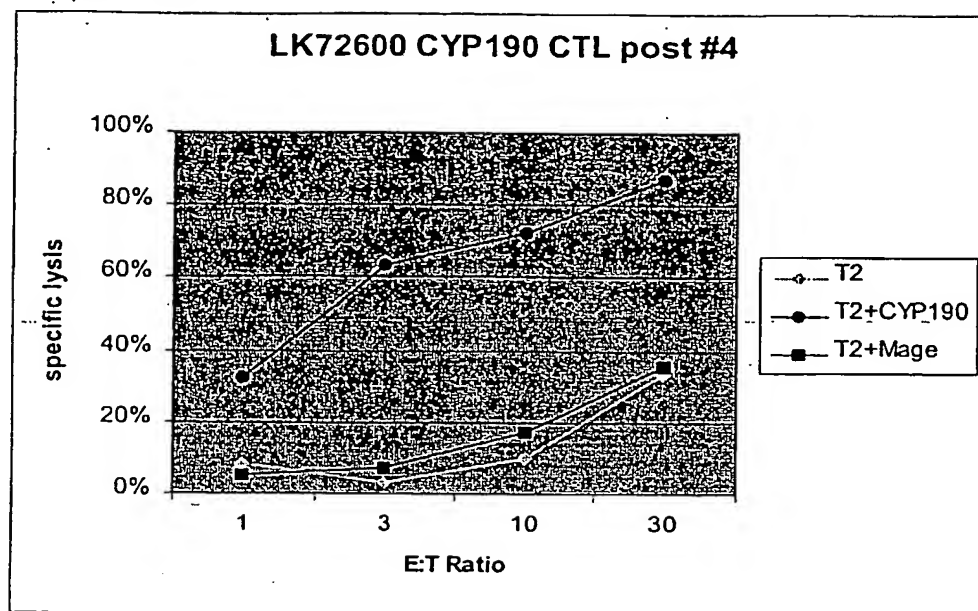


FIGURE 13B

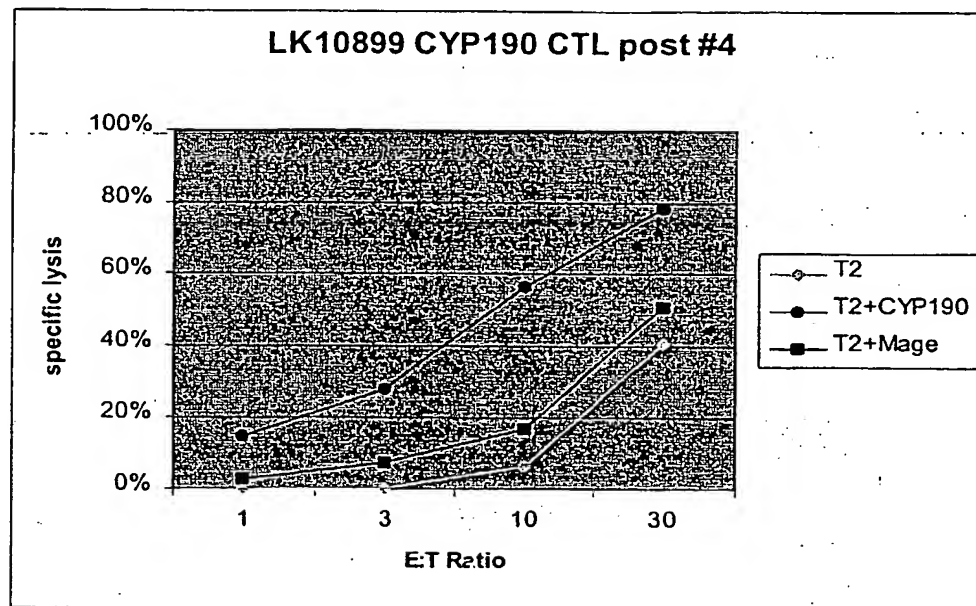


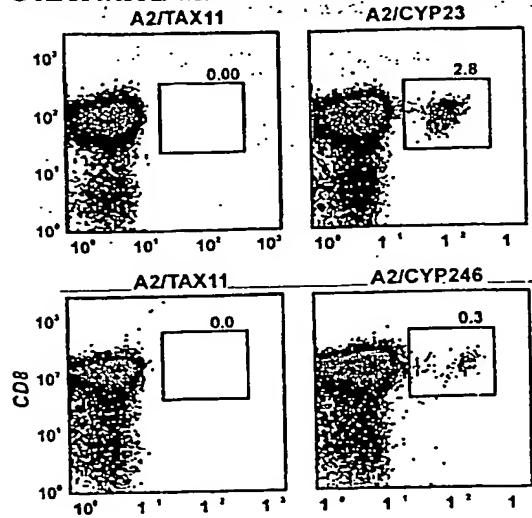
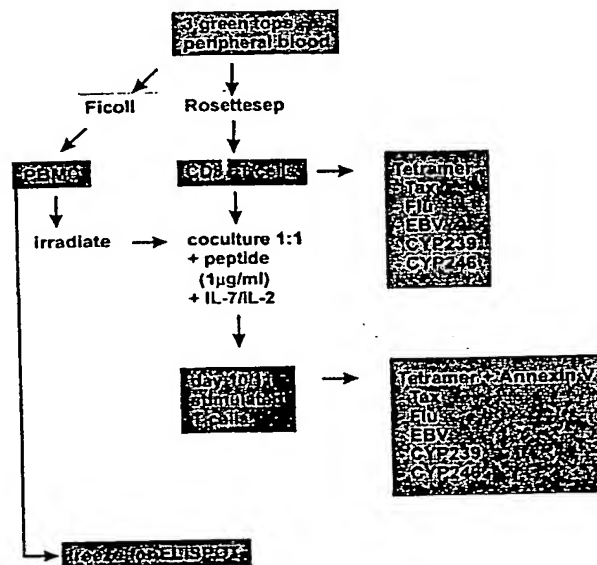
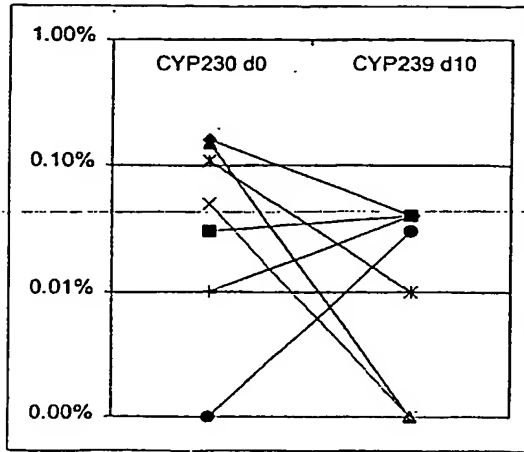
FIGURE 14**Generation and verification of CYP1B1 specific tetramers****FIGURE 15****Analysis of MM pB samples**

FIGURE 16

CYP239



CYP246

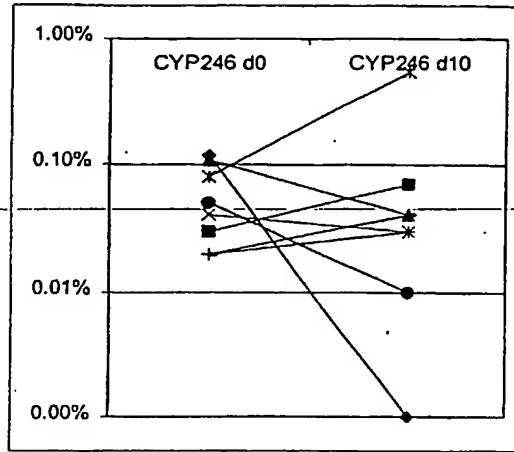
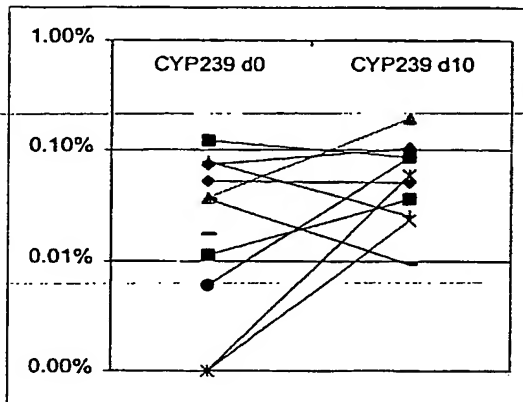
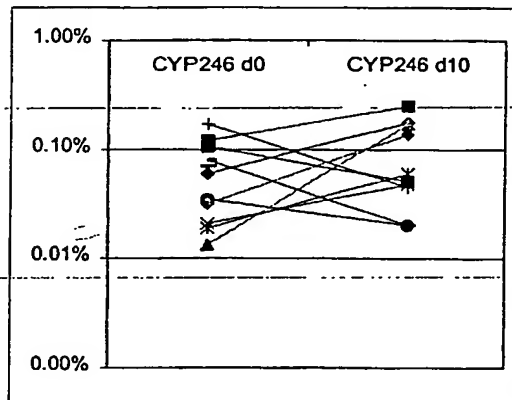


FIGURE 17

CYP239



CYP246



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International Bureau



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(71) Applicants (for all designated States except US):
DANA-FARBER CANCER INSTITUTE, INC.
[US/US]; 44 Binney Street, Boston, MA 02115 (US).
TRUSTEES OF BOSTON UNIVERSITY [US/US]; 147
Bay State Road, Boston, MA 02215 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SCHULTZE,**

Joachim, L. [DE/US]; 37 Auburn Street, Brookline, MA
02146 (US). **VONDERHEIDE, Robert, H.** [DE/US];
Apartment 801, 1284 Beacon Street, Brookline, MA
02115 (US). **SHERR, David** [US/US]; 39 Hastings Street,
West Roxbury, MA 02132 (US). **NADLER, Lee, M.**
[US/US]; 36 Cross Hill Road, Newton, MA 02159 (US).
MAECKER, Britta [DE/US]; 368 Longwood Avenue,
#21, Boston, MA 02215 (US). **VON BERGWELT-BAIL-**
DON, Michael [DE/US]; 24 A Prentiss Street, Cambridge,
MA 02140 (US).

(74) Agent: **CLARK, Paul, T.**; Clark & Elbing LLP, 176 Fed-
eral Street, Boston, MA 02110-2214 (US).

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(57) Abstract: The invention provides methods for conducting cancer immunotherapy and diagnosis using cytochrome P450 1B1 and peptide fragments thereof.

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US CL : 424/93.21, 93.7, 184.1; 435/252.3, 325

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.21, 93.7, 184.1; 435/252.3, 325

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	Database DERWENT, Accession No. 2000-365402, HAHN et al. Universal tumor-associated antigens such as telomerase catalytic subunit capable of binding major histocompatibility complex molecule useful for diagnosis, prevention and treatment of cancer. Abstract, WO 00/25813 A1 (DANA FARBER CANCER INSTITUTE, INC) 11 May 2000, see abstract	1-6, 19-23 and 28
A, P	Database CAPLUS on ACS, Accession No. 2000:494217, HEIDEL et al. Cytochrome P4501B1 mediates induction of bone marrow cytotoxicity and preleukemia cells in mice treated with 7,12-dimethylbenz[a]anthracene. Cancer Res. 2000. Vol. 60. No. 13, pages 3454-3460, see abstract.	1-6, 19-23 and 28



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

13 APRIL 2001

Date of mailing of the international search report

14 JUN 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

SUSAN UNGAR

TERRY J. DEY

PARALEGAL SPECIALIST

Telephone No.

(703) TECHNOLOGY CENTER 1500

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/31513

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database CAPLUS on ACS, Accession No. 1999:203774, SPENCER et al. Quantitative analysis of constitutive and 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin-induced cytochrome P450 1B1 expression in human lymphocytes. Cancer Epidemiology, Biomarkers Prev., 1999, Vol 8, No. 2 pages 139-146, see abstract	1-6, 19-23 and 28

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/31513

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-6, 19-23 and 28

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/31513

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

PIR_66, BIOSIS, BIOTECHNO, CAPLUS, EMBASE, ESBIODBASE, GENBANK, LIFESCI, MEDLINE, SCISEARCH, TOXLINE, TOXLIT

search terms: 450 CYP1b1, gene, treat, antigen presenting cell, cytotoxic, T-lymphocyte

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-6, and 19-23 and 28, drawn to a method of treating a patient with cytotoxic T cells and cytotoxic T cells.

Group II, claim(s) 7-10 and 19-23, drawn to a method of treating patients with an antigen presenting cell that activates cytotoxic T lymphocytes.

Group III, claim(s) 11-14 and 19-23, drawn to a method of treating a patient comprising administering a peptide of CYT p450 1B1.

Group IV, claim(s) 15-18 and 19-23, drawn to a method of treating a patient comprising administering a nucleic acid encoding CYT P450 1B1 or a peptide thereof.

Group V, claim(s) 24-25, drawn to a method of assessing the level of immunity in a patient.

Group VI, claim(s) 26-27, drawn to drawn to a peptide.

Group VI, claim(s) 29, drawn to an ex vivo generated antigen presenting cell.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

The claims are deemed to correspond to the species listed above in the following manner:

The following claims are generic:

Group I, claim 1, the species are

Species (a) SEQ ID NO:1

Species (b) SEQ ID NO:2

Species (c) SEQ ID NO:3

Species (d) SEQ ID NO:4, all of claim 23

Group II, claim 1, the species are

Species (a) SEQ ID NO:1

Species (b) SEQ ID NO:2

Species (c) SEQ ID NO:3

Species (d) SEQ ID NO:4, all of claim 23

Group III, claim 1, the species are

Species (a) SEQ ID NO:1

Species (b) SEQ ID NO:2

Species (c) SEQ ID NO:3

Species (d) SEQ ID NO:4, all of claim 23

Group IV, claim 1, the species are

Species (a) SEQ ID NO:1

Species (b) SEQ ID NO:2

Species (c) SEQ ID NO:3

Species (d) SEQ ID NO:4, all of claim 23

INTERNATIONAL SEARCH REPORT

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Group VI, claim 1, the species are
Species (a) SEQ ID NO:1
Species (b) SEQ ID NO:2
Species (c) SEQ ID NO:3
Species (d) SEQ ID NO:4, all of claim 27

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The first invention claimed, claims 1-6, 20-23 and 28 is considered the main invention. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories thereto will be considered as the main invention of the claims, see PCT Article 17(3)(a) and 1.476(c). After that, all other products and methods will be broken out as separate groups. (See 37 CFR 1.475(d). All of the other groups are drawn to products of methods not recited in the main invention.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The species recited relate to products with different sequences and therefore different structures and functions.